A 21-year-old health care worker with a history of bulimia nervosa is brought to the hospital due to generalized weakness and dizziness. She reports no vomiting or laxative use. On admission, she is fully responsive. Blood pressure is 110/60 mm Hg and pulse is 102/min. Physical examination shows dry mucous membranes. Urine screening for diuretics reveals a large amount of furosemide. Which of the following sets of laboratory findings would most likely suggest that this patient is abusing furosemide to lose weight?

	Serum bicarbonate	Serum chloride	Urine sodium	Urine potassium
A.	↑	↓	↑	↑
B.	↓	↓	↑	↑
C.	↓	Normal	Normal	↓
D.	↓	↓	↑	↓
E.	↑	↑	Normal	↑

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	Serum bicarbonate	Serum chloride	Urine sodium	Urine potassium
✓ A. (68%)	↑	↓	↑	↑
B. (15%)	↓	↓	↑	↑
C. (1%)	↓	Normal	Normal	↓
D. (6%)	↓	↓	↑	↓
E. (7%)	↑	↑	Normal	↑

Omitted
Correct answer
A

68%
Answered correctly

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Time Spent

04/20/2020
Last Updated

Explanation

Explanation

Hypokalemic, hypochloremic metabolic alkalosis	
Common etiologies	• Gastric suction or severe vomiting • Loop or thiazide diuretic overuse
Pathophysiology	• Gastric or renal H^+ losses **initiate** alkalosis • Volume depletion activates RAAS • ↑ renal K^+ & H^+ losses cause hypokalemia & **worsen** alkalosis • Relatively greater loss of Cl^- than Na^+ → profound Cl^- depletion • ↓ Cl^- impairs renal HCO_3^- excretion to **perpetuate** alkalosis
Management	• Remove or treat initiating factor • Cl^- repletion with normal saline corrects alkalosis

RAAS = renin-angiotensin-aldosterone system.

Loop diuretics (eg, furosemide) are sometimes abused by patients with eating disorders (eg, anorexia nervosa, bulimia nervosa) in an effort to lose weight. These drugs **inhibit the Na^+-K^+-2Cl^- transporter** in the loop of Henle, resulting in increased urinary excretion of Na^+, Cl^-, K^+, and water. These changes in electrolyte handling also increase renal H^+ excretion, leading to **metabolic alkalosis** (elevated serum HCO_3^-). Overuse of loop diuretics leads to massive electrolyte and fluid losses with **intravascular volume depletion** and activation of the renin-angiotensin-aldosterone system. This secondary hyperaldosteronism stimulates increased Na^+ reabsorption in the renal tubular collecting duct, as well as a lesser degree of passive Cl^- reabsorption. The relatively high loss of Cl^- that occurs is responsible for a **characteristic hypochloremia**.

Secondary hyperaldosteronism also stimulates increased K^+ and H^+ excretion in the collecting duct, exacerbating the **hypokalemia** and metabolic alkalosis. The alkalosis is further compounded by an angiotensin II-mediated increase in proximal tubule sodium bicarbonate reabsorption. **Chloride depletion** then **perpetuates the alkalosis** because low Cl^- levels in the tubular lumen impair HCO_3^- excretion via the pendrin Cl^-/HCO_3^- exchanger on beta intercalated cells in the collecting duct.

The **urine electrolyte** findings in loop diuretic abuse depend on how recently the medication was last ingested. Within several hours after

Loop diuretics (eg, furosemide) are sometimes abused by patients with eating disorders (eg, anorexia nervosa, bulimia nervosa) in an effort to lose weight. These drugs **inhibit the Na^+-K^+-$2Cl^-$ transporter** in the loop of Henle, resulting in increased urinary excretion of Na^+, Cl^-, K^+, and water. These changes in electrolyte handling also increase renal H^+ excretion, leading to **metabolic alkalosis** (elevated serum HCO_3^-). Overuse of loop diuretics leads to massive electrolyte and fluid losses with **intravascular volume depletion** and activation of the renin-angiotensin-aldosterone system. This secondary hyperaldosteronism stimulates increased Na^+ reabsorption in the renal tubular collecting duct, as well as a lesser degree of passive Cl^- reabsorption. The relatively high loss of Cl^- that occurs is responsible for a **characteristic hypochloremia**.

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The **urine electrolyte** findings in loop diuretic abuse depend on how recently the medication was last ingested. Within several hours after ingestion (as in this patient with positive urine screening), **increased urine Na^+, Cl^-, and K^+** is expected. Once the medication effect wears off, urine Na^+ and urine Cl^- are low as the kidneys attempt to increase blood volume. Urine K^+ is likely to remain increased due to ongoing aldosterone-mediated losses **(Choice C)**.

(Choices B, D, and E) Because Cl^- and HCO_3^- are the most abundant anions in the body, they are the primary determinants of total body electronegativity. Therefore, when one of these anions is depleted the kidneys and intestines retain the other to maintain electronegative balance. This results in a typical inverse relationship between serum Cl^- and serum HCO_3^- levels (when one is low the other tends to be elevated). The presence of additional anions in the body (eg, anion gap metabolic acidosis) may disrupt this relationship.

Educational objective:
Overuse or abuse of loop diuretics (eg, furosemide) characteristically causes hypokalemic, hypochloremic metabolic alkalosis. Urine electrolyte findings depend on how recently the diuretic was last ingested; increased urine Na^+, Cl^-, and K^+ are expected with recent ingestion.

References

- Loop diuretics.

Pharmacology Renal, Urinary Systems & Electrolytes Metabolic alkalosis

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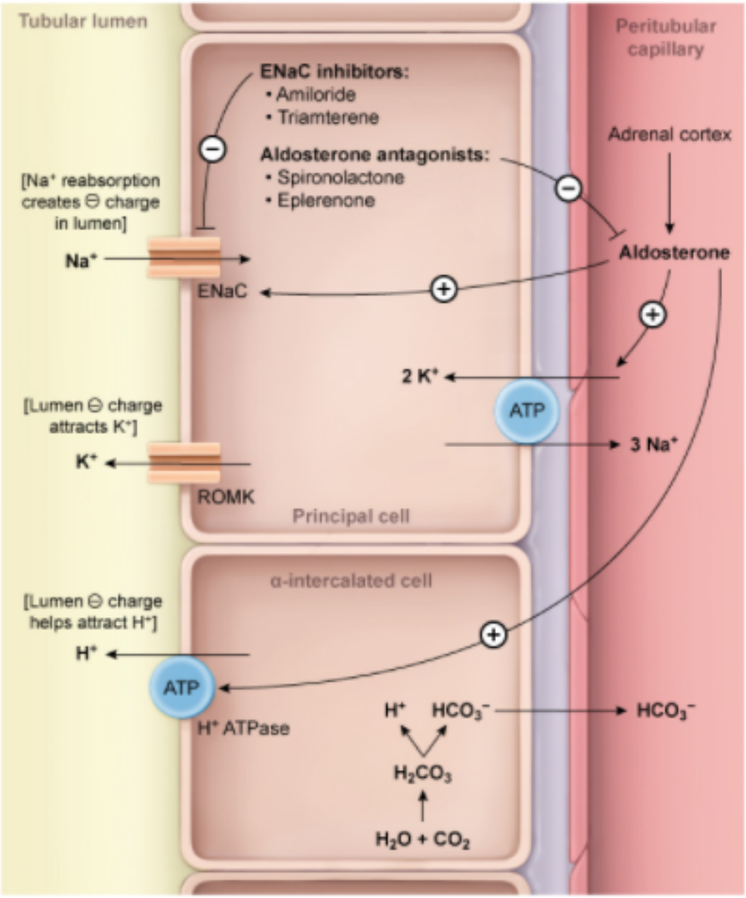
Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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Pharmacology Renal, Urinary Systems & Electrolytes Metabolic alkalosis

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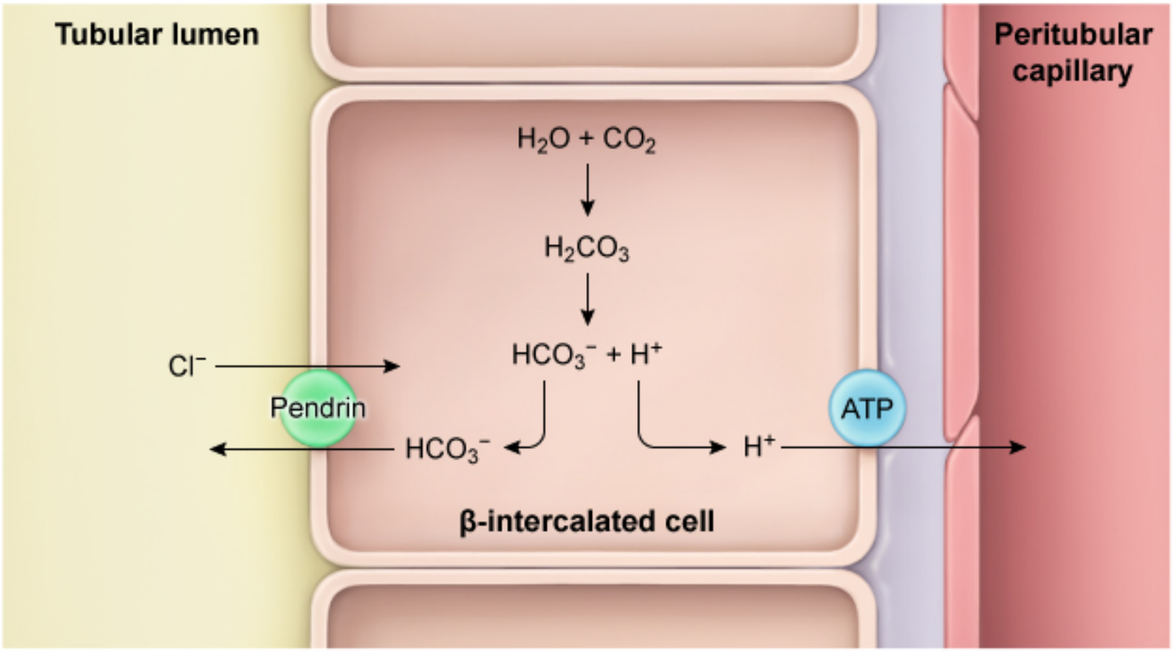
Exhibit Display

Pendrin chloride/bicarbonate exchanger



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Pharmacology Renal, Urinary Systems & Electrolytes Metabolic alkalosis

A 68-year-old man comes to the emergency department due to a 1-week history of increasing leg and abdominal swelling. The patient has a history of pulmonary hypertension and cor pulmonale from advanced chronic obstructive pulmonary disease. Other medical conditions include hypertension and gout. Physical examination shows scattered rhonchi, prolonged expiratory phase of expiration, mild ascites, and extensive edema of the abdominal wall and lower extremities. The patient is hospitalized and intravenous loop diuretic therapy is begun. Two days later, acetazolamide is added to his treatment regimen. Which of the following most likely prompted the additional therapy in this patient?

A. Hyperuricemia

B. Hypokalemia

C. Inadequate diuresis

D. Metabolic alkalosis

E. Prerenal azotemia

Submit

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- A. Hyperuricemia (6%)
- B. Hypokalemia (6%)
- C. Inadequate diuresis (8%)
- ✓ D. Metabolic alkalosis (76%)
- E. Prerenal azotemia (1%)

Omitted
Correct answer
D

76%
Answered correctly

02 secs
Time Spent

04/15/2020
Last Updated

Explanation

Diuretic effects on total body electrolyte levels					
Diuretic type	Na^+	K^+	HCO_3^-	Ca^{2+}	Uric acid
Loop (eg, furosemide)	↓↓↓	↓↓	↑↑	↓	↑

Diuretic effects on total body electrolyte levels					
Diuretic type	Na^+	K^+	HCO_3^-	Ca^{2+}	**Uric acid**
Loop (eg, furosemide)	↓↓↓	↓↓	↑↑	↓	↑
Thiazide (eg, HCTZ, metolazone)	↓↓	↓	↑	↑	↑
Potassium sparing (eg, spironolactone, amiloride)	↓	↑	↓	—	—
Carbonic anhydrase inhibitor (eg, acetazolamide)	↓	↓	↓	—	—
HCTZ = hydrochlorothiazide.					

Loop diuretics (eg, furosemide) inhibit the Na^+-K^+-$2Cl^-$ transporter in the ascending loop of Henle to stimulate potent excretion of Na^+ and water and reduce total body fluid volume. Electrolyte abnormalities are common with the use of loop diuretics; **metabolic alkalosis** occurs due to the following mechanisms:

- Sodium and water losses induced by diuretic therapy cause increased aldosterone-mediated **renal excretion of H^+** and K^+.
- Loop diuretics cause relatively greater loss of Cl^- than Na^+, resulting in decreased total body electronegativity. In response, the **kidneys retain more HCO_3^-**, the second most abundant anion in the body, to maintain electrochemical balance.

This metabolic alkalosis can have important implications because it stimulates **compensatory hypoventilation** that may **hinder weaning** from mechanical ventilation in critically ill patients. **Carbonic anhydrase inhibitors** (eg, acetazolamide) help offset the metabolic alkalosis; these drugs inhibit the reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule, leading to **increased HCO_3^- excretion**. The metabolic acidosis that is generated reduces blood alkalinity to **help normalize pH**.

(Choice A) Loop diuretics increase renal uric acid reabsorption and are associated with hyperuricemia (increased blood uric acid level) and

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(Choice A) Loop diuretics increase renal uric acid reabsorption and are associated with hyperuricemia (increased blood uric acid level) and increased risk of gout. Probenecid blocks proximal tubule uric acid reabsorption and may reduce loop diuretic–associated hyperuricemia.

(Choice B) Hypokalemia is a common adverse effect of loop diuretics. The addition of a potassium-sparing diuretic (eg, spironolactone) can help offset the hypokalemia by reducing K^+ secretion in the collecting tubules. Potassium-sparing diuretics also encourage a mild metabolic acidosis, but less so than carbonic anhydrase inhibitors.

(Choice C) Carbonic anhydrase inhibitors have only a weak diuretic effect because most of the Na^+ blocked from reabsorption in the proximal tubules is reabsorbed more distally. Thiazide diuretics (eg, metolazone) act distally in the nephron and potentiate the diuretic effect of loop diuretics by blocking the reabsorption of increased Na^+ delivered to the distal convoluted tubules, producing a profound synergistic diuresis.

(Choice E) Loop diuretics can cause significant intravascular volume depletion with reduced renal perfusion and consequent renal retention of urea (evidenced by blood urea nitrogen/creatinine ratio >20). This prerenal azotemia is improved by temporary cessation of diuretics to allow intravascular volume to reaccumulate, but it is not improved by carbonic anhydrase inhibitor therapy.

Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) block the reabsorption of sodium bicarbonate in the proximal tubule to cause metabolic acidosis. These drugs can be used to help offset the metabolic alkalosis caused by loop diuretics.

HCTZ = hydrochlorothiazide.

Exhibit Display

Site of inhibition for various diuretics

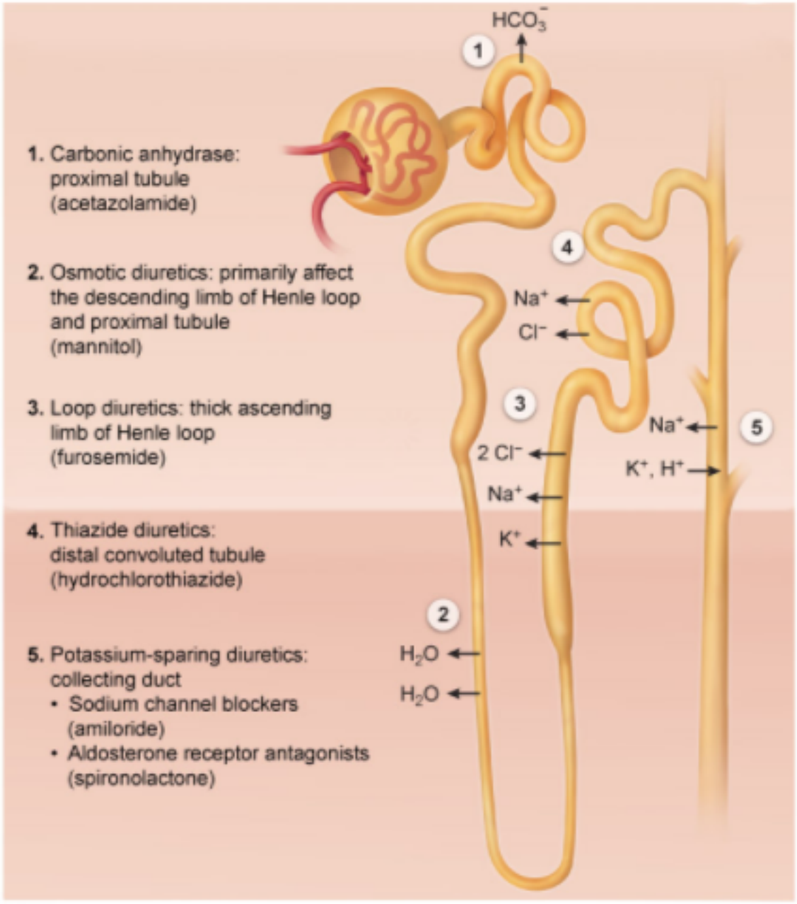

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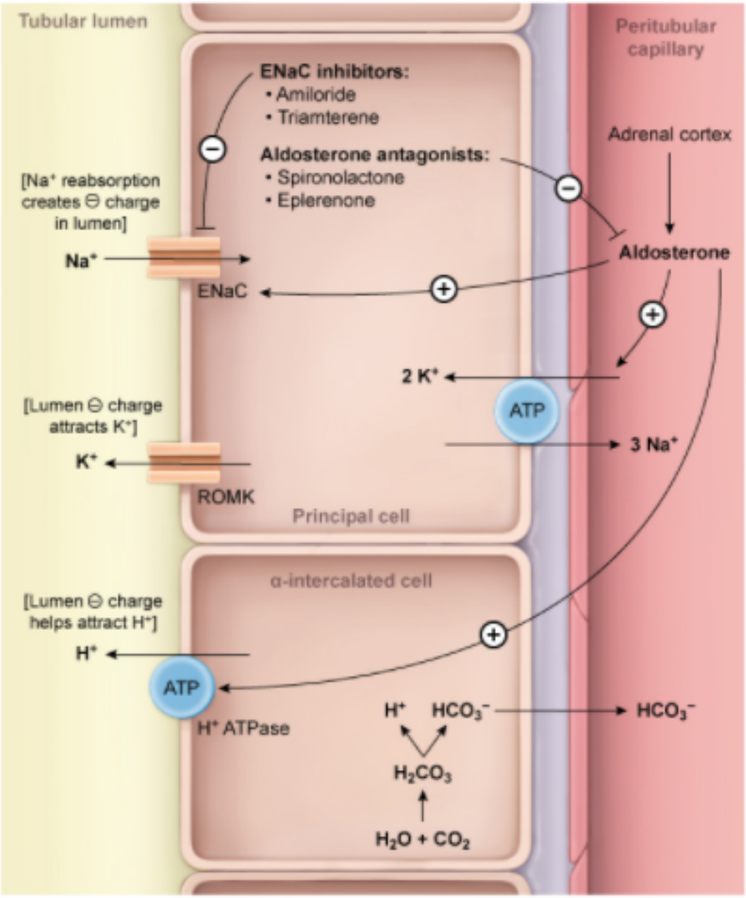
Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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(Choice A) Loop diuretics increase renal uric acid reabsorption and are associated with hyperuricemia (increased blood uric acid level) and increased risk of gout. Probenecid blocks proximal tubule uric acid reabsorption and may reduce loop diuretic–associated hyperuricemia.

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Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) block the reabsorption of sodium bicarbonate in the proximal tubule to cause metabolic acidosis. These drugs can be used to help offset the metabolic alkalosis caused by loop diuretics.

Pharmacology	Renal, Urinary Systems & Electrolytes	Acetazolamide
Subject	System	Topic

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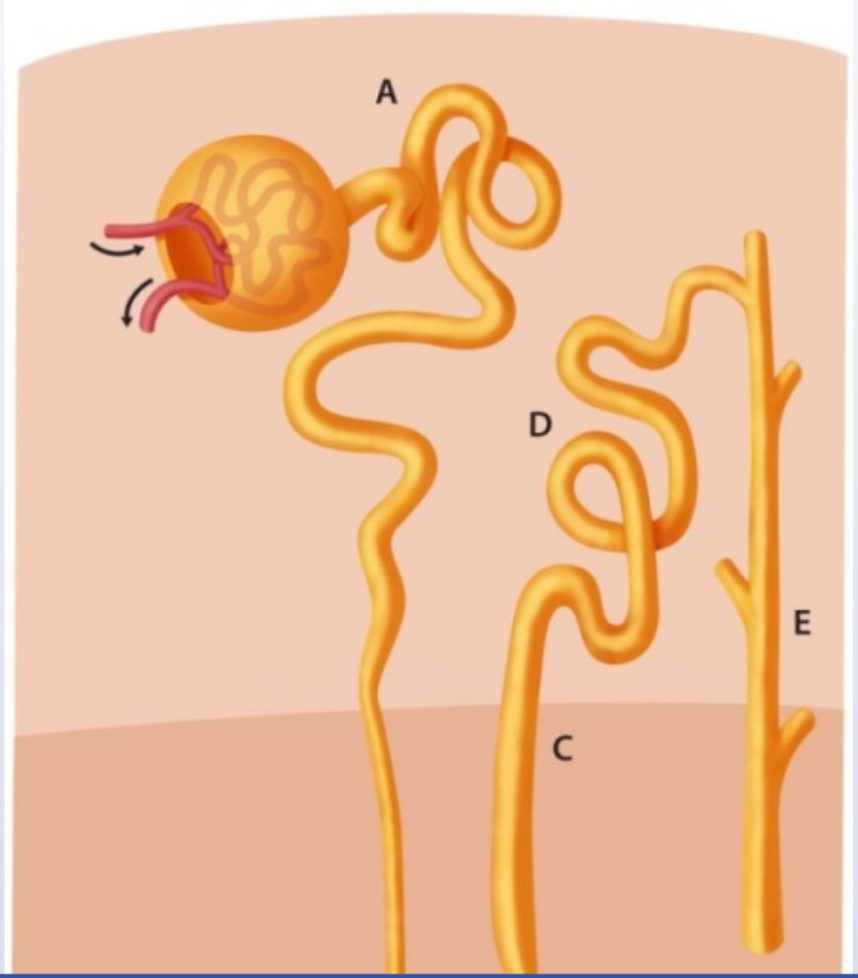
A 62-year-old man comes to the emergency department with severe shortness of breath and orthopnea. His medical history is significant for long-standing hypertension and myocardial infarction a year ago. Physical examination reveals elevated jugular venous pressure, crackles on lung auscultation, and pitting edema of the lower extremities. The patient is given a medication and experiences brisk diuresis with significant symptom relief. The drug most likely used to treat this patient's condition predominantly acts on which of the following nephron segments?



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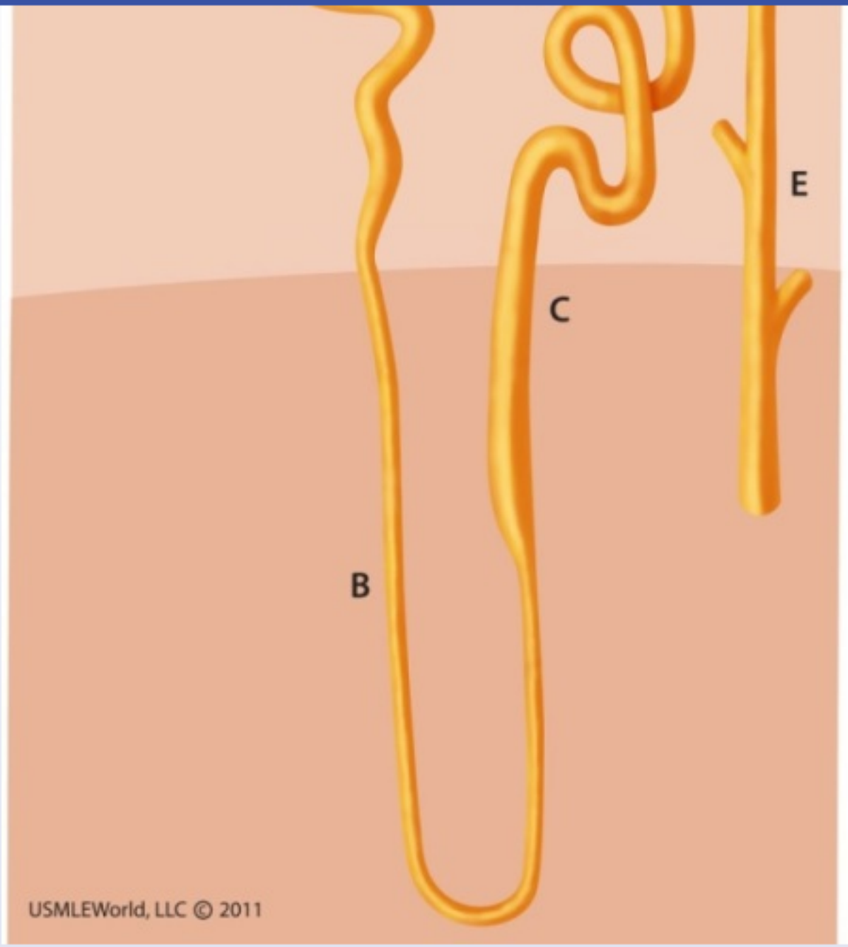

A. A

B. B

C. C

D. D

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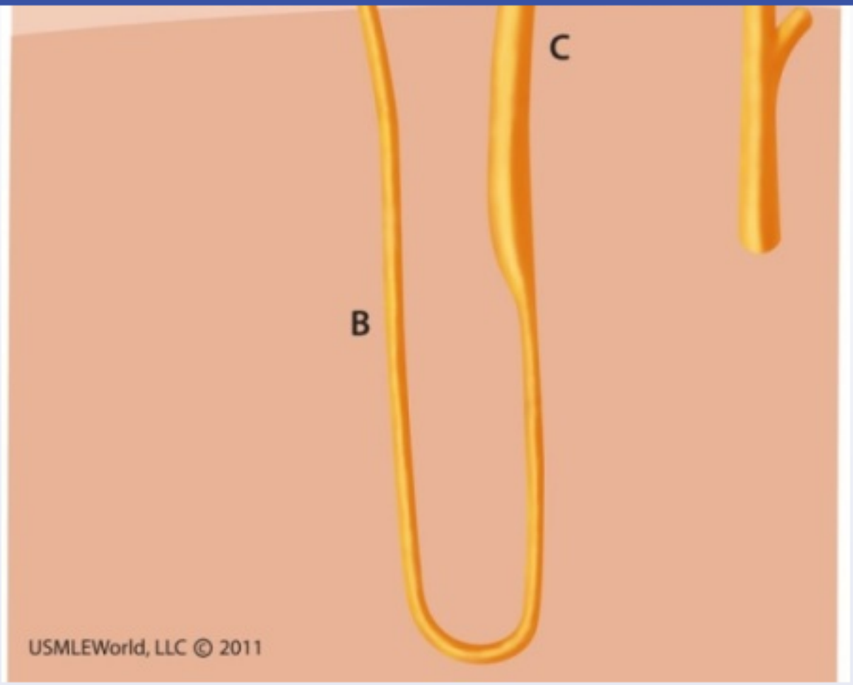

A. A

B. B

C. C

D. D

E. E

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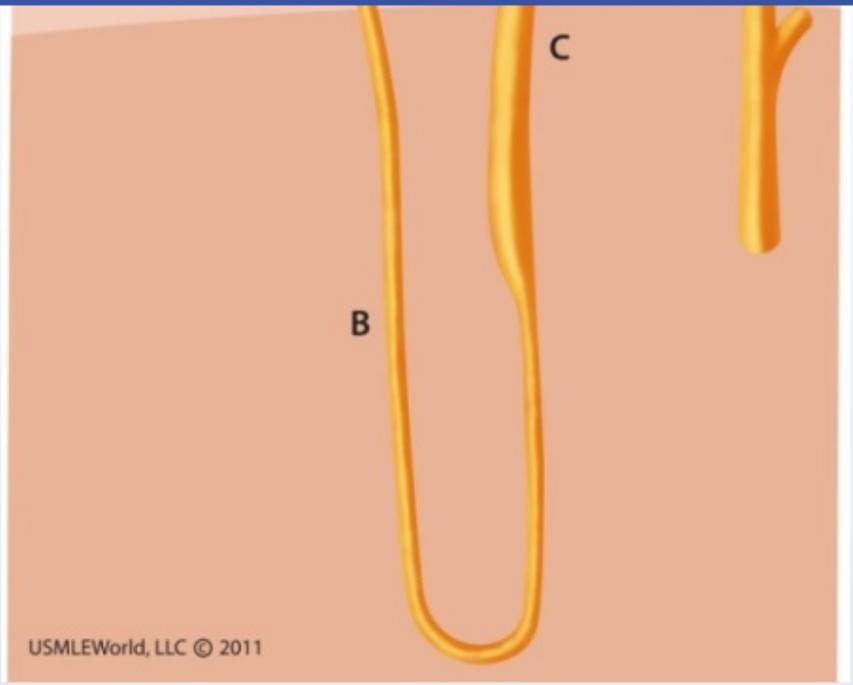

A. A (3%)

B. B (8%)

✓ C. C (75%)

D. D (7%)

E. E (4%)

Omitted
Correct answer

75%
Answered correctly

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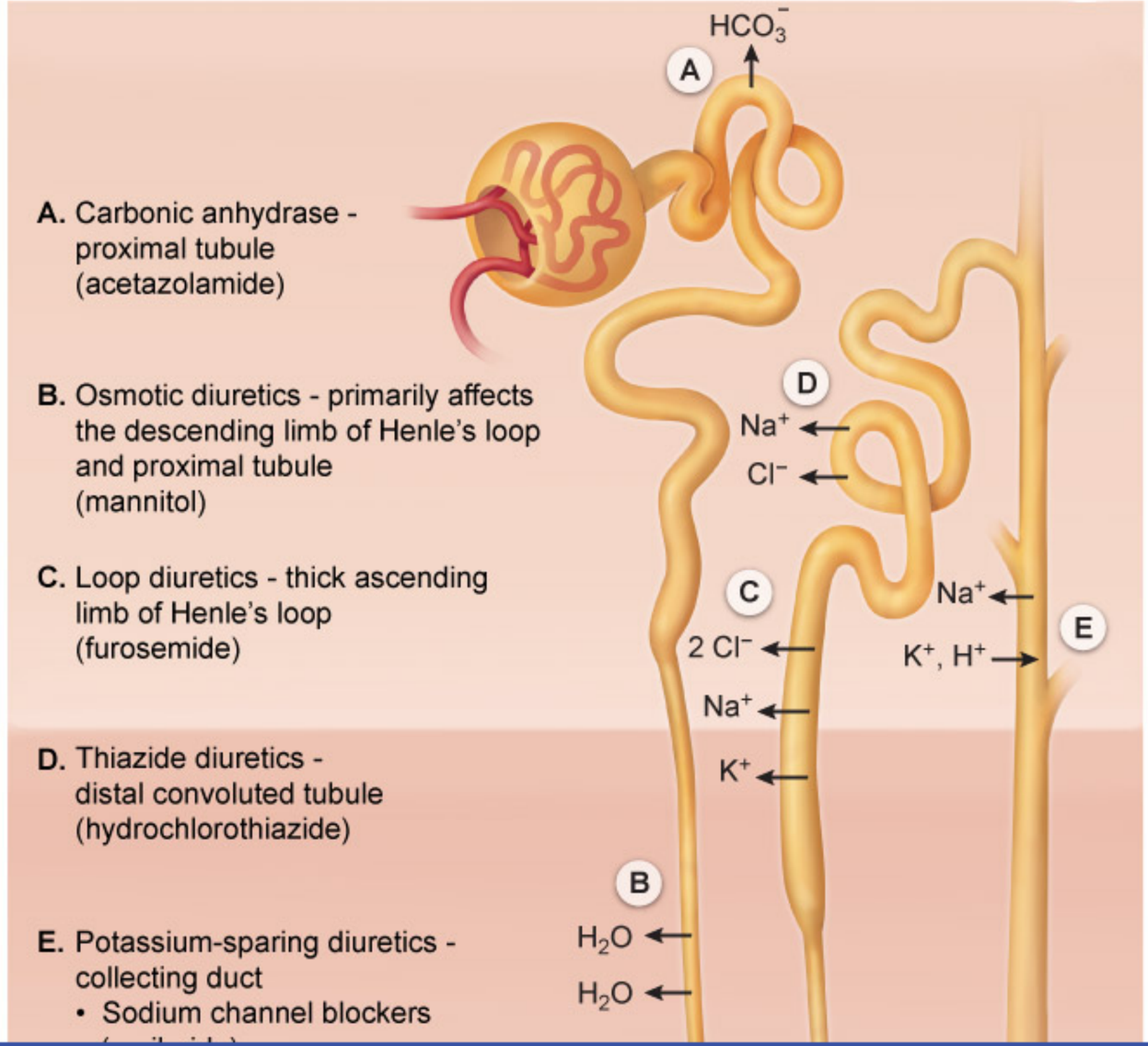
Time Spent

01/12/2020
Last Updated

Site of action for various diuretics



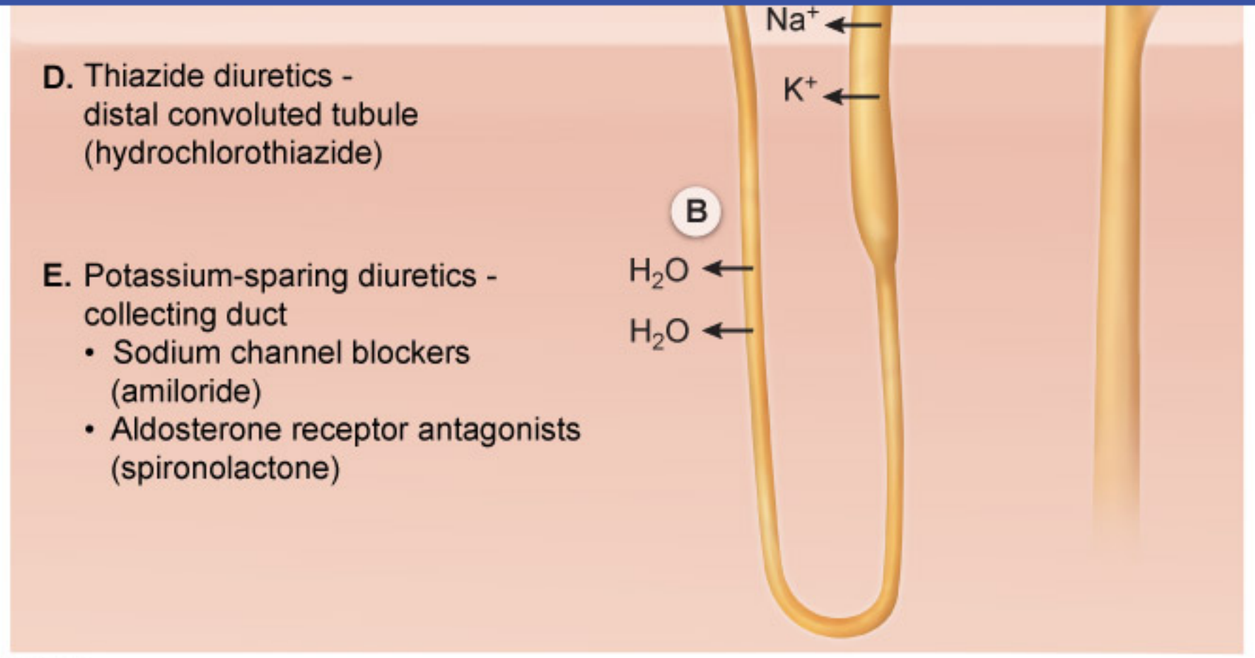
A. Carbonic anhydrase - proximal tubule (acetazolamide)

B. Osmotic diuretics - primarily affects the descending limb of Henle's loop and proximal tubule (mannitol)

C. Loop diuretics - thick ascending limb of Henle's loop (furosemide)

D. Thiazide diuretics - distal convoluted tubule (hydrochlorothiazide)

E. Potassium-sparing diuretics - collecting duct
- Sodium channel blockers



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This patient with dyspnea and volume overload (ie, elevated jugular venous pressure, edema, lung crackles) has **acute decompensated heart failure**. Patients with heart failure and volume overload are typically treated with **loop diuretics** due to their potent natriuretic effect, which helps reduce vascular congestion and peripheral edema.

Loop diuretics (eg, furosemide, torsemide, bumetanide) inhibit the **Na-K-2Cl symporter** in the apical membranes of cells in the **thick ascending limb of Henle's loop**. Blockade of Na^+ and Cl^- reabsorption from the tubular lumen decreases the medullary concentration gradient, impairing the kidney's ability to concentrate urine and increasing the overall excretion of Na^+, Cl^-, and H_2O. Adverse effects of loop diuretics include electrolyte abnormalities (eg, hypokalemia, hypomagnesemia) and ototoxicity.

(Choice A) Carbonic anhydrase inhibitors (acetazolamide) block the reabsorption of NaCl and $NaHCO_3$ in the proximal tubule. They are weak diuretic agents typically used to treat glaucoma and altitude sickness.

(Choice B) Mannitol is a nonreabsorbable sugar alcohol that functions as an osmotic diuretic by decreasing sodium and water reabsorption by

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(Choice D) Thiazide diuretics act by inhibiting NaCl reabsorption in the distal convoluted tubule. Compared to the loop of Henle, this segment reabsorbs only a small proportion of the filtered NaCl load, leading to a smaller natriuretic effect than loop diuretics. Thiazides are mostly used to treat hypertension and are not as effective as loop diuretics for reducing volume overload in heart failure.

(Choice E) The collecting tubules and ducts are the primary site of action of sodium channel blockers (eg, amiloride, triamterene) and aldosterone receptor antagonists (eg, spironolactone, eplerenone). These are weak diuretics that are not effective for diuresis in patients with decompensated heart failure. However, long-term use of aldosterone receptor antagonists improves survival in patients with severe left ventricular systolic dysfunction.

Educational objective:
Loop diuretics act by inhibiting the Na-K-2Cl cotransporter in the thick ascending limb of the loop of Henle, increasing Na^+, Cl^-, and H_2O excretion. They are the most potent diuretics and are used as first-line therapy for rapid relief of symptoms in patients with acute decompensated heart failure.

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Pharmacology	Renal, Urinary Systems & Electrolytes	Loop diuretics
Subject	System	Topic

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A 36-year-old man comes to the emergency department due to severe, acute knee pain that awoke him from sleep. He has a history of end-stage renal disease for which he underwent a renal transplant 8 weeks ago. The patient takes an immunosuppressive regimen containing cyclosporine, low-dose prednisone, and mycophenolate mofetil. He visited his nephrologist last week and was told that his blood test results were normal. Temperature is 37.5 C (99.5 F), blood pressure is 136/78 mm Hg, and pulse is 88/min. Examination shows redness, warmth, and a small effusion in the left knee. Passive range of motion at the knee causes severe pain. Microscopic examination of joint fluid from the knee shows numerous neutrophils as well as both intra- and extracellular crystals as shown in the exhibit. Which of the following mechanisms is most likely responsible for this patient's acute symptoms?

A. Decreased urinary excretion of uric acid

B. Increased production of uric acid

C. Rapid drop in blood uric acid levels

D. Release of nucleic acids from apoptotic cells

E. Volume depletion and decreased renal perfusion

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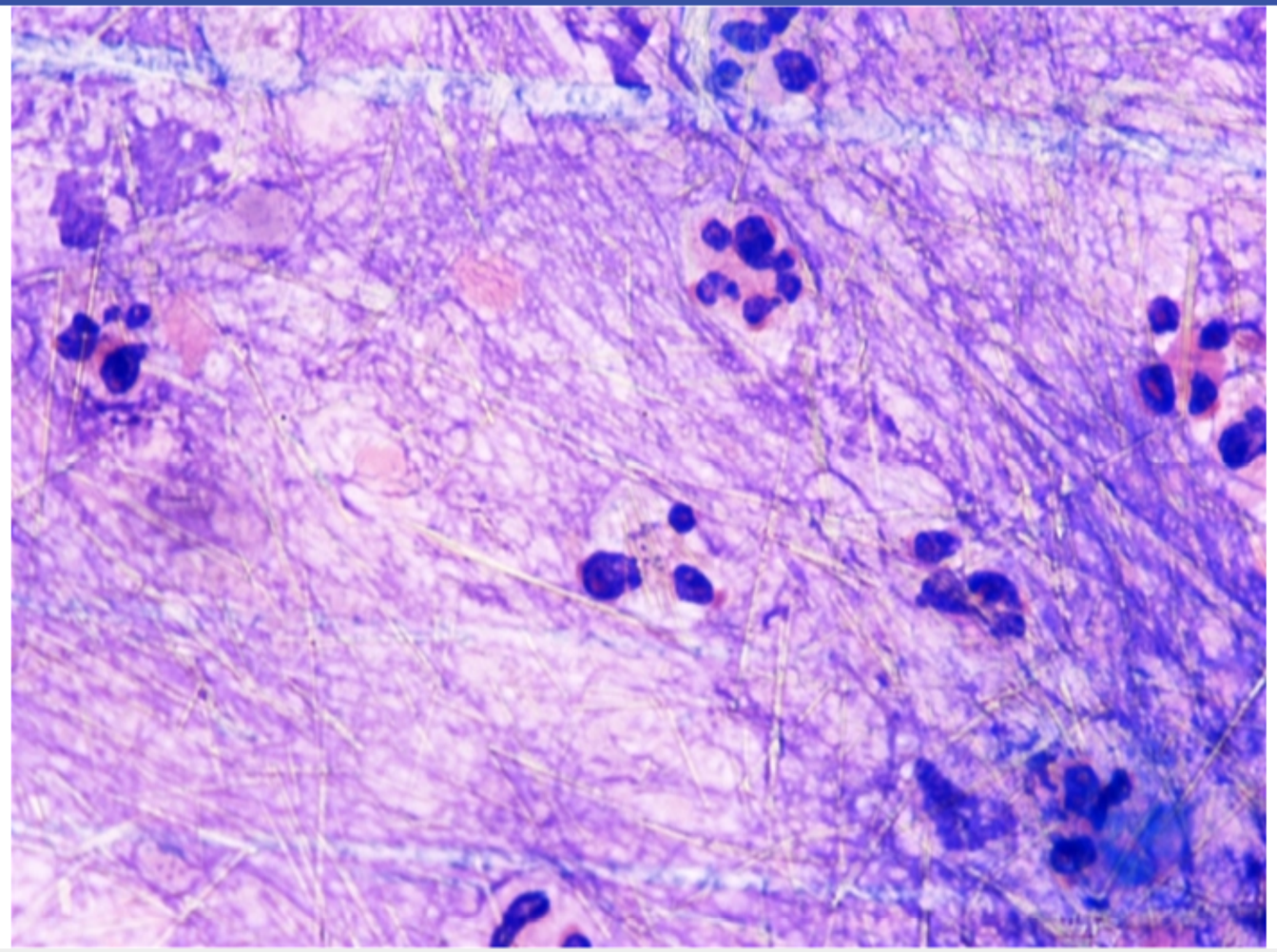
Exhibit Display



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A 36-year-old man comes to the emergency department due to severe, acute knee pain that awoke him from sleep. He has a history of end-stage renal disease for which he underwent a renal transplant 8 weeks ago. The patient takes an immunosuppressive regimen containing cyclosporine, low-dose prednisone, and mycophenolate mofetil. He visited his nephrologist last week and was told that his blood test results were normal. Temperature is 37.5 C (99.5 F), blood pressure is 136/78 mm Hg, and pulse is 88/min. Examination shows redness, warmth, and a small effusion in the left knee. Passive range of motion at the knee causes severe pain. Microscopic examination of joint fluid from the knee shows numerous neutrophils as well as both intra- and extracellular crystals as shown in the exhibit. Which of the following mechanisms is most likely responsible for this patient's acute symptoms?

- ✓ A. Decreased urinary excretion of uric acid (47%)
- B. Increased production of uric acid (24%)
- C. Rapid drop in blood uric acid levels (2%)
- D. Release of nucleic acids from apoptotic cells (22%)
- E. Volume depletion and decreased renal perfusion (2%)

Omitted
Correct answer
A

47%
Answered correctly

09 secs
Time Spent

05/09/2020
Last Updated

Explanation

Medications associated with gout	
	• Diuretics (eg, hydrochlorothiazide, furosemide)

Medications associated with gout	
Reduced uric acid excretion	• Diuretics (eg, hydrochlorothiazide, furosemide) • Salicylates (eg, low-dose aspirin) • ACE inhibitors (eg, lisinopril) • Cyclosporine
Increased uric acid production	• Cytotoxic chemotherapy agents (tumor lysis syndrome)
Rapid decline in uric acid levels	• Xanthine oxidase inhibitors (eg, allopurinol) • Uricosuric drugs (eg, probenecid)

This patient has acute monoarticular arthritis of the knee with synovial fluid evidence of inflammation and needle-shaped (monosodium urate) crystals, indicating a diagnosis of **gout**. Gout develops in patients with **hyperuricemia** and is associated with several risk factors including excessive alcohol intake, meat/seafood consumption, chronic kidney disease, and certain medications.

Cyclosporine is a common cause of gout exacerbations in patients who have undergone solid organ transplantation, particularly renal transplantation. This medication **impairs renal excretion of uric acid**, resulting in hyperuricemia. Although high doses of systemic glucocorticoids (eg, prednisone) can be used to treat acute gout, the low doses used for immunosuppression in patients who have undergone transplantation are usually not sufficient to prevent gout flares.

(Choice B) Increased production of uric acid is commonly due to a purine-rich diet (eg, red meat, seafood), excessive alcohol intake, fructose-sweetened beverage intake, or disorders associated with increased cell turnover (eg, myeloproliferative disorders, cancers).

(Choice C) Urate-lowering agents (eg, allopurinol) are used to prevent recurrent gout but can occasionally precipitate a gout flare due to rapid declines in blood uric acid levels, which can disrupt preexisting crystal deposits and increase their immunogenicity. This patient is not taking a medication that lowers uric acid levels.

(Choice D) Patients who have malignancy associated with high tumor burdens (eg, acute lymphoblastic leukemia) can develop tumor lysis syndrome when cytotoxic chemotherapy is initiated. The massive release of nucleic acids into the circulation (from lysed cells) increases serum uric acid levels (due to catabolism of purine nucleic acids) and can precipitate gout.

This patient has acute monoarticular arthritis of the knee with synovial fluid evidence of inflammation and needle-shaped (monosodium urate) crystals, indicating a diagnosis of **gout**. Gout develops in patients with **hyperuricemia** and is associated with several risk factors including excessive alcohol intake, meat/seafood consumption, chronic kidney disease, and certain medications.

Cyclosporine is a common cause of gout exacerbations in patients who have undergone solid organ transplantation, particularly renal transplantation. This medication **impairs renal excretion of uric acid**, resulting in hyperuricemia. Although high doses of systemic glucocorticoids (eg, prednisone) can be used to treat acute gout, the low doses used for immunosuppression in patients who have undergone transplantation are usually not sufficient to prevent gout flares.

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(Choice C) Urate-lowering agents (eg, allopurinol) are used to prevent recurrent gout but can occasionally precipitate a gout flare due to rapid declines in blood uric acid levels, which can disrupt preexisting crystal deposits and increase their immunogenicity. This patient is not taking a medication that lowers uric acid levels.

(Choice D) Patients who have malignancy associated with high tumor burdens (eg, acute lymphoblastic leukemia) can develop tumor lysis syndrome when cytotoxic chemotherapy is initiated. The massive release of nucleic acids into the circulation (from lysed cells) increases serum uric acid levels (due to catabolism of purine nucleic acids) and can precipitate gout.

(Choice E) Diuretics (eg, furosemide, hydrochlorothiazide) can be associated with gout as these medications reduce urate excretion in the proximal tubule and also cause volume depletion leading to decreased renal perfusion and filtration of uric acid.

Educational objective:
Patients undergoing solid organ transplantation are at increased risk of gout due to medications that impair renal clearance of uric acid. Cyclosporine is particularly associated with gout in the post-transplantation period due to decreased uric acid excretion.

References

- Gout and organ transplantation.

Pharmacology Renal, Urinary Systems & Electrolytes Gout

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A 34-year-old kidney transplant patient treated with cyclosporine comes to the office due to nausea and anorexia. The patient underwent transplantation 6 months ago and had been doing well until recently. On examination, his blood pressure is 160/96 mm Hg. There is no tenderness at the site of the transplanted kidney. Serum creatinine is 3.4 mg/dL, and the serum cyclosporine level is markedly increased. A month ago, he had normal blood pressure and normal levels of cyclosporine and serum creatinine. Further questioning reveals that the patient has been drinking increased amounts of grapefruit juice lately as part of an attempt to improve his overall health. Which of the following mechanisms is most likely responsible for this patient's current condition?

A. Alteration of gastric acidity

B. Inhibition of cytochrome P450 enzymes in the gut wall

C. Modification of transmembrane drug transport

D. Pharmacodynamic potentiation

E. Reduction of plasma protein binding

Submit

A 34-year-old kidney transplant patient treated with cyclosporine comes to the office due to nausea and anorexia. The patient underwent transplantation 6 months ago and had been doing well until recently. On examination, his blood pressure is 160/96 mm Hg. There is no tenderness at the site of the transplanted kidney. Serum creatinine is 3.4 mg/dL, and the serum cyclosporine level is markedly increased. A month ago, he had normal blood pressure and normal levels of cyclosporine and serum creatinine. Further questioning reveals that the patient has been drinking increased amounts of grapefruit juice lately as part of an attempt to improve his overall health. Which of the following mechanisms is most likely responsible for this patient's current condition?

- A. Alteration of gastric acidity (1%)
- ✓ B. Inhibition of cytochrome P450 enzymes in the gut wall (81%)
- C. Modification of transmembrane drug transport (2%)
- D. Pharmacodynamic potentiation (13%)
- E. Reduction of plasma protein binding (1%)

Omitted
Correct answer
B

81%
Answered correctly

01 sec
Time Spent

05/20/2020
Last Updated

Explanation

This patient's new-onset hypertension and elevated levels of serum creatinine and cyclosporine are suggestive of acute **calcineurin inhibitor nephrotoxicity**. Calcineurin inhibitors such as cyclosporine cause dose-dependent renal vasoconstriction and tubular cell damage, which can precipitate acute renal failure.

Cyclosporine is extensively metabolized by the liver and gastrointestinal tract via the cytochrome P450 system, specifically the **CYP3A**

This patient's new-onset hypertension and elevated levels of serum creatinine and cyclosporine are suggestive of acute **calcineurin inhibitor nephrotoxicity**. Calcineurin inhibitors such as cyclosporine cause dose-dependent renal vasoconstriction and tubular cell damage, which can precipitate acute renal failure.

Cyclosporine is extensively metabolized by the liver and gastrointestinal tract via the cytochrome P450 system, specifically the **CYP3A isoenzymes**. Inhibition of intestinal P450 enzymes by the furocoumarins present in **grapefruit juice** can slow the breakdown of drugs metabolized by this pathway, raising circulating levels of the affected drugs. Medications with a narrow therapeutic index (eg, cyclosporine) have the highest risk of toxicity.

(Choice A) Changes in gastric pH do not significantly affect the oral bioavailability of cyclosporine.

(Choice C) Transmembrane cyclosporine transport is not affected by grapefruit juice.

(Choice D) Pharmacodynamic potentiation is defined as a greater than additive effect that occurs when 2 different drugs are administered simultaneously due to functional interactions within the target tissues. Grapefruit juice increases the effect of cyclosporine by slowing its metabolism, which is a pharmacokinetic mechanism.

(Choice E) A decrease in plasma protein binding could lower the apparent volume of distribution of a fixed dose of cyclosporine, thereby increasing the amount of free drug in circulation. However, grapefruit juice does not influence the binding of cyclosporine to plasma proteins.

Educational objective:
Calcineurin inhibitor nephrotoxicity with resultant impairment of renal function is the most significant adverse effect of cyclosporine. Cytochrome P450 3A (CYP3A) is responsible for cyclosporine metabolism in the small intestine and liver. Grapefruit juice inhibits this enzyme and increases the nephrotoxicity of cyclosporine by raising circulating drug levels (pharmacokinetic interaction).

References

- The effect of grapefruit juice on cyclosporine and prednisone metabolism in transplant patients.

Pharmacology	Renal, Urinary Systems & Electrolytes	Drug interaction
Subject	System	Topic

A 59-year-old man who is being treated for hypercholesterolemia, diabetes, and hypertension comes to the physician for a scheduled follow-up visit three weeks after starting a new medication. He has no new complaints. Blood work drawn yesterday shows an interim increase in potassium from 4.8 mEq/L to 5.2 mEq/L and a creatinine elevation from 1.2 mg/dL to 1.6 mg/dL. Administration of which of the following drugs is most likely responsible for the change in this patient's renal function?

A. Lisinopril
B. Metoprolol
C. Atorvastatin
D. Hydrochlorothiazide
E. Furosemide
F. Metformin
G. Prazosin

Submit

A 59-year-old man who is being treated for hypercholesterolemia, diabetes, and hypertension comes to the physician for a scheduled follow-up visit three weeks after starting a new medication. He has no new complaints. Blood work drawn yesterday shows an interim increase in potassium from 4.8 mEq/L to 5.2 mEq/L and a creatinine elevation from 1.2 mg/dL to 1.6 mg/dL. Administration of which of the following drugs is most likely responsible for the change in this patient's renal function?

- ✓ A. Lisinopril (61%)
- B. Metoprolol (3%)
- C. Atorvastatin (7%)
- D. Hydrochlorothiazide (7%)
- E. Furosemide (6%)
- F. Metformin (11%)
- G. Prazosin (1%)

Omitted
Correct answer
A

61%
Answered correctly

05 secs
Time Spent

05/29/2020
Last Updated

Explanation

Angiotensin-converting enzyme (ACE) inhibitors (typically named "-pril") are one of the most important agents in treating hypertension, heart failure, and renal failure with or without proteinuria. They work by preventing the conversion of angiotensin I to angiotensin II. This prevents the efferent arteriole from constricting more than the afferent arteriole, thus decreasing the glomerular pressure and glomerular filtration rate (GFR). It

Angiotensin-converting enzyme (ACE) inhibitors (typically named "-pril") are one of the most important agents in treating hypertension, heart failure, and renal failure with or without proteinuria. They work by preventing the conversion of angiotensin I to angiotensin II. This prevents the efferent arteriole from constricting more than the afferent arteriole, thus decreasing the glomerular pressure and glomerular filtration rate (GFR). It is expected for the GFR to decrease in all patients initially. Most clinicians are generally not concerned by this unless the creatinine increases by greater than 30% because the long-term benefits of ACE inhibitors are well studied. Other common side-effects of ACE inhibitors include hyperkalemia and cough.

(Choice B) Metoprolol is a beta-blocker. Typical side-effects include bradycardia and erectile dysfunction. Although beta blockers act upon the beta-1 receptors of the juxtaglomerular cells to reduce renin secretion, their use generally does not have a clinically significant effect on the GFR.

(Choice C) Atorvastatin is an HMG-CoA reductase inhibitor; worrisome side-effects include muscle toxicity and hepatic dysfunction. Statins can uncommonly cause rhabdomyolysis, particularly when used in combination with fibrates or cyclosporin. However, massive rhabdomyolysis leading to acute kidney injury would most likely produce additional signs and symptoms such as myalgias, muscle weakness, dark urine, and elevated creatine kinase.

(Choices D and E) Hydrochlorothiazide is a *potassium-wasting* thiazide diuretic that may decrease GFR if it results in volume depletion and pre-renal azotemia. Furosemide is also *potassium-wasting* loop diuretic.

(Choice F) Metformin itself does not have nephrotoxic side effects. However, impaired renal function or recent IV contrast administration may reduce metformin excretion, resulting in systemic accumulation and possible lactic acidosis.

(Choice G) Prazosin is an alpha-1 adrenergic antagonist that is used in the treatment of hypertension. It does not decrease the GFR.

Educational objective:
Common side-effects of ACE-inhibitors include decreased glomerular filtration rate (GFR), hyperkalemia, and cough. Angioedema is a rare, but life-threatening, side-effect.

Pharmacology	Renal, Urinary Systems & Electrolytes	Hyperkalemia
Subject	System	Topic

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A 57-year-old man comes to the emergency department with severe right-sided eye pain and ipsilateral headache. Furthermore, the patient reports severe nausea and describes seeing "halos" around objects. After initial treatment with the appropriate medication, the severity of his pain decreases. He also experiences increased diuresis with highly alkaline urine. The drug used to treat this patient's eye condition predominantly acts on which of the following nephron segments?

- A. A
- B. B
- C. C
- D. D
- E. E

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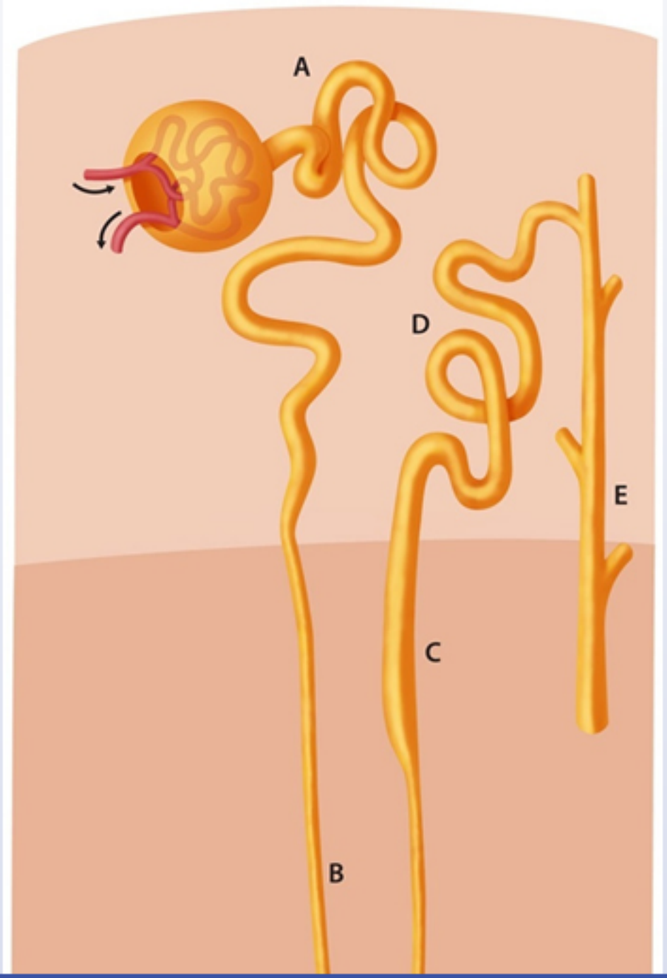

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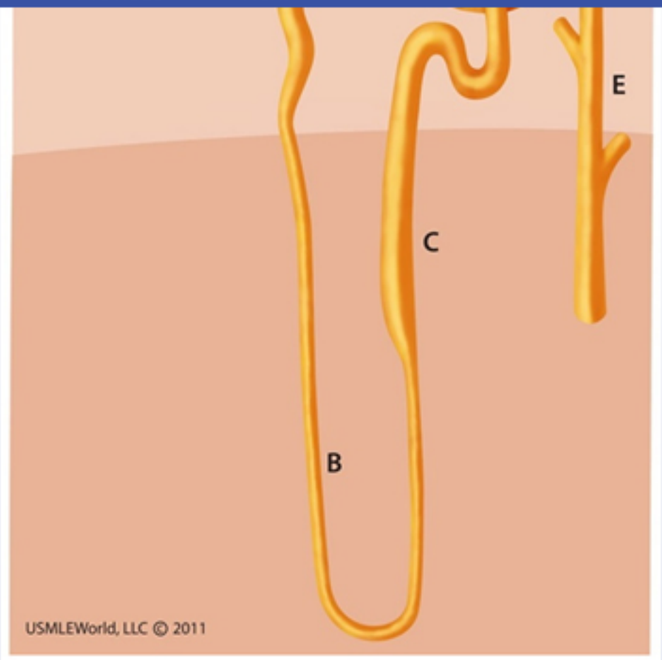

A. A

B. B

C. C

D. D

E. E

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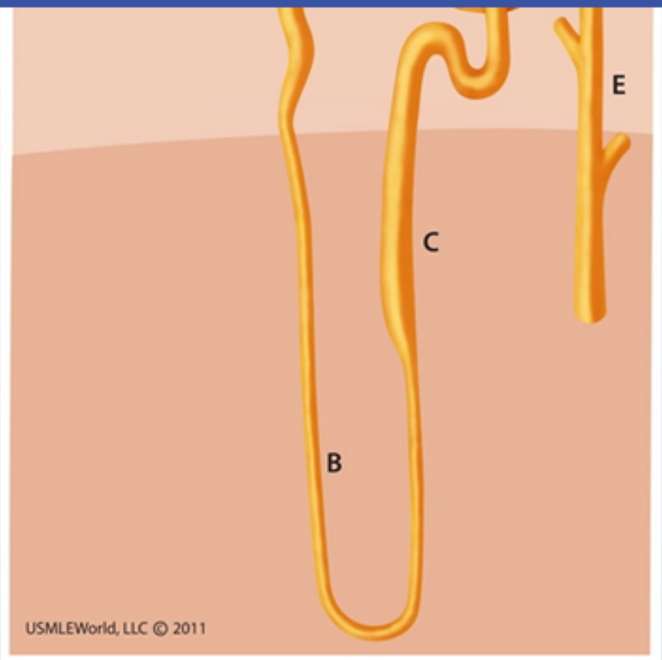

- ✓ A. A (77%)
- B. B (4%)
- C. C (4%)
- D. D (5%)
- E. E (8%)

Omitted
Correct answer

77%
Answered correctly

12 mins, 06 secs
Time Spent

01/21/2020
Last Updated

This patient has acute angle-closure glaucoma and has been treated with acetazolamide. Acetazolamide is a diuretic that works by inhibiting the enzyme carbonic anhydrase. Carbonic anhydrase is found in high concentrations in the proximal tubule and is responsible for catalyzing reactions necessary for $NaHCO_3$ reabsorption. By inhibiting carbonic anhydrase, acetazolamide and other carbonic anhydrase inhibitors effectively block HCO_3^- reabsorption in the proximal tubules. This results in enhanced HCO_3^- and water excretion as well as increased urinary pH and potential metabolic acidosis.

Carbonic anhydrase is also present in the eyes, pancreas, gastrointestinal tract, CNS, and red blood cells. In eye tissues, carbonic anhydrase modulates HCO_3^- formation in the aqueous humor. Inhibition of carbonic anhydrase will decrease HCO_3^- and aqueous humor formation; thus, a number of carbonic anhydrase inhibitors are used to relieve intraocular pressures in open-angle and angle-closure glaucoma. Common side effects of carbonic anhydrase inhibitors include somnolence, paresthesias, and urine alkalinization. Rare side effects include metabolic acidosis, dehydration, hypokalemia, and hyponatremia.

(Choice B) The descending limb of the loop of Henle carries fluid from the proximal tubule to the ascending limb of the loop of Henle in the medulla. The descending limb is very permeable to water, allowing water to diffuse into interstitial fluids to produce a more concentrated tubular fluid.

(Choice C) Loop diuretics work in the thick ascending limb and are the most potent diuretics.

(Choice D) The distal tubule actively transports Na^+ and Cl^- and is impermeable to water. Thiazide diuretics work in the distal tubule.

(Choice E) The collecting duct system includes the collecting tubules and ducts. Here, aldosterone and ADH make final adjustments to electrolytes and water content. Potassium-sparing diuretics and aldosterone antagonists also work in the collecting duct.

Educational objective:
Carbonic anhydrase is found in high concentrations in the proximal tubule and is responsible for catalyzing reactions necessary for $NaHCO_3$ reabsorption. Acetazolamide is a diuretic that works by inhibiting carbonic anhydrase, which effectively blocks $NaHCO_3$ and water reabsorption in the proximal tubules resulting in urinary bicarbonate wasting. Carbonic anhydrase inhibitors are also used to relieve intraocular pressure in open-angle and angle-closure glaucoma.

References

- Ophthaproblem. Acute angle-closure glaucoma.

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References

- Ophthaproblem. Acute angle-closure glaucoma.

Pharmacology	Renal, Urinary Systems & Electrolytes	Acetazolamide
Subject	System	Topic

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A 55-year-old with woman with stage IV chronic kidney disease due to type 2 diabetes mellitus comes to the office for a follow-up visit. Blood pressure is 140/90 mm Hg and pulse is 78/min. BMI is 31 kg/m^2. Laboratory results are as follows:

Hemoglobin	10.5 g/dL
Calcium	8.8 mg/dL
Albumin	3.7 g/dL
Phosphorus	7.2 mg/dL
Creatinine	3.3 mg/dL
Blood urea nitrogen	88 mg/dL
Parathyroid hormone	100 pg/mL (normal: 10-65)

The patient's serum phosphorus has been persistently elevated despite strict dietary phosphate restriction. Treatment with sevelamer is initiated. This medication reduces the serum phosphorus level by which of the following mechanisms?

A. Blocking of vitamin D receptors
B. Decreased intestinal absorption of phosphorus
C. Reduction of proximal renal tubular reabsorption of phosphorus
D. Stimulation of fibroblast growth factor 23 release
E. Suppression of parathyroid hormone secretion
F. Transcellular movement of phosphorus

Submit

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Submit

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Creatinine	3.3 mg/dL
Blood urea nitrogen	88 mg/dL
Parathyroid hormone	100 pg/mL (normal: 10-65)

The patient's serum phosphorus has been persistently elevated despite strict dietary phosphate restriction. Treatment with sevelamer is initiated. This medication reduces the serum phosphorus level by which of the following mechanisms?

A. Blocking of vitamin D receptors (2%)
✓ B. Decreased intestinal absorption of phosphorus (61%)
C. Reduction of proximal renal tubular reabsorption of phosphorus (21%)
D. Stimulation of fibroblast growth factor 23 release (4%)
E. Suppression of parathyroid hormone secretion (6%)
F. Transcellular movement of phosphorus (3%)

Omitted
Correct answer

61%
Answered correctly

05 secs
Time Spent

05/09/2020
Last Updated

Chronic kidney disease (CKD) often causes **hyperphosphatemia** due to the impaired ability of the kidneys to excrete phosphorus. Hyperphosphatemia is thought to be the inciting event in the onset of CKD-related mineral bone disorder. Elevated blood phosphate triggers the release of fibroblast growth factor 23 from bone, which lowers calcitriol production and intestinal calcium absorption. Reduced circulating calcium, along with hyperphosphatemia, leads to secondary hyperparathyroidism.

Dietary phosphorus restriction is recommended for patients with CKD. However, oral **phosphate binders** are usually needed if dietary restriction is not sufficient to lower phosphate levels. Phosphate binders can be calcium containing (eg, calcium carbonate/acetate) or non–calcium containing (eg, sevelamer, lanthanum). **Sevelamer** is a **nonabsorbable anion-exchange resin** that binds intestinal phosphate to **reduce systemic absorption**. The resulting complex is eliminated in the feces.

(Choice A) Vitamin D receptor antagonists are largely experimental compounds that have been considered for the treatment of Paget disease of bone. Most patients with CKD benefit from vitamin D supplementation due to decreased renal formation of 1,25-dihydroxyvitamin D.

(Choices C, D, and F) Parathyroid hormone induces internalization and destruction of type IIa sodium/phosphate cotransporters (NPT2) in the proximal renal tubule. *NPT2* gene expression is downregulated by fibroblast growth factor 23. These processes lead to decreased transcellular transport (and therefore decreased reabsorption) of phosphate in the renal tubules.

(Choice E) Parathyroid hormone functions to reduce phosphate reabsorption by the kidney; reduced secretion would worsen, not correct, hyperphosphatemia. Sevelamer reduces circulating serum phosphorus by blocking intestinal absorption, which helps to mitigate secondary hyperparathyroidism.

Educational objective:
Chronic kidney disease can cause hyperphosphatemia due to decreased renal excretion of phosphorus. Dietary phosphorus restriction is recommended, but oral phosphate binders are often needed. Sevelamer is a nonabsorbable anion-exchange resin that binds intestinal phosphate to reduce absorption.

References

- Sevelamer carbonate: a review in hyperphosphataemia in adults with chronic kidney disease.

Pharmacology Renal, Urinary Systems & Electrolytes Chronic kidney disease

A 57-year-old man comes to the office for a follow-up appointment. He has a history of systolic heart failure, which has been managed with appropriate medical therapy. The patient experiences significant functional impairment at his baseline and is able to walk only short distances. His most recent echocardiogram showed a left ventricular ejection fraction of 30% (normal ≥55%). The physician decides to start him on spironolactone. The addition of this medication to the patient's current regimen is most likely to cause a decrease in which of the following renal functions?

A. Hydrogen ion generation by the proximal convoluted tubule

B. Hydrogen ion secretion from the collecting tubules

C. $Na^+/K^+/2Cl^-$ cotransport in the thick ascending limb

D. Proximal convoluted tubule brush border transport capacity

E. Urea reabsorption in the collecting tubules

Submit

A 57-year-old man comes to the office for a follow-up appointment. He has a history of systolic heart failure, which has been managed with appropriate medical therapy. The patient experiences significant functional impairment at his baseline and is able to walk only short distances. His most recent echocardiogram showed a left ventricular ejection fraction of 30% (normal ≥55%). The physician decides to start him on spironolactone. The addition of this medication to the patient's current regimen is most likely to cause a decrease in which of the following renal functions?

- A. Hydrogen ion generation by the proximal convoluted tubule (2%)
- ✓ B. Hydrogen ion secretion from the collecting tubules (79%)
- C. $Na^+/K^+/2Cl^-$ cotransport in the thick ascending limb (7%)
- D. Proximal convoluted tubule brush border transport capacity (1%)
- E. Urea reabsorption in the collecting tubules (8%)

Omitted
Correct answer
B

79%
Answered correctly

02 secs
Time Spent

03/10/2020
Last Updated

Explanation

Site of inhibition for various diuretics

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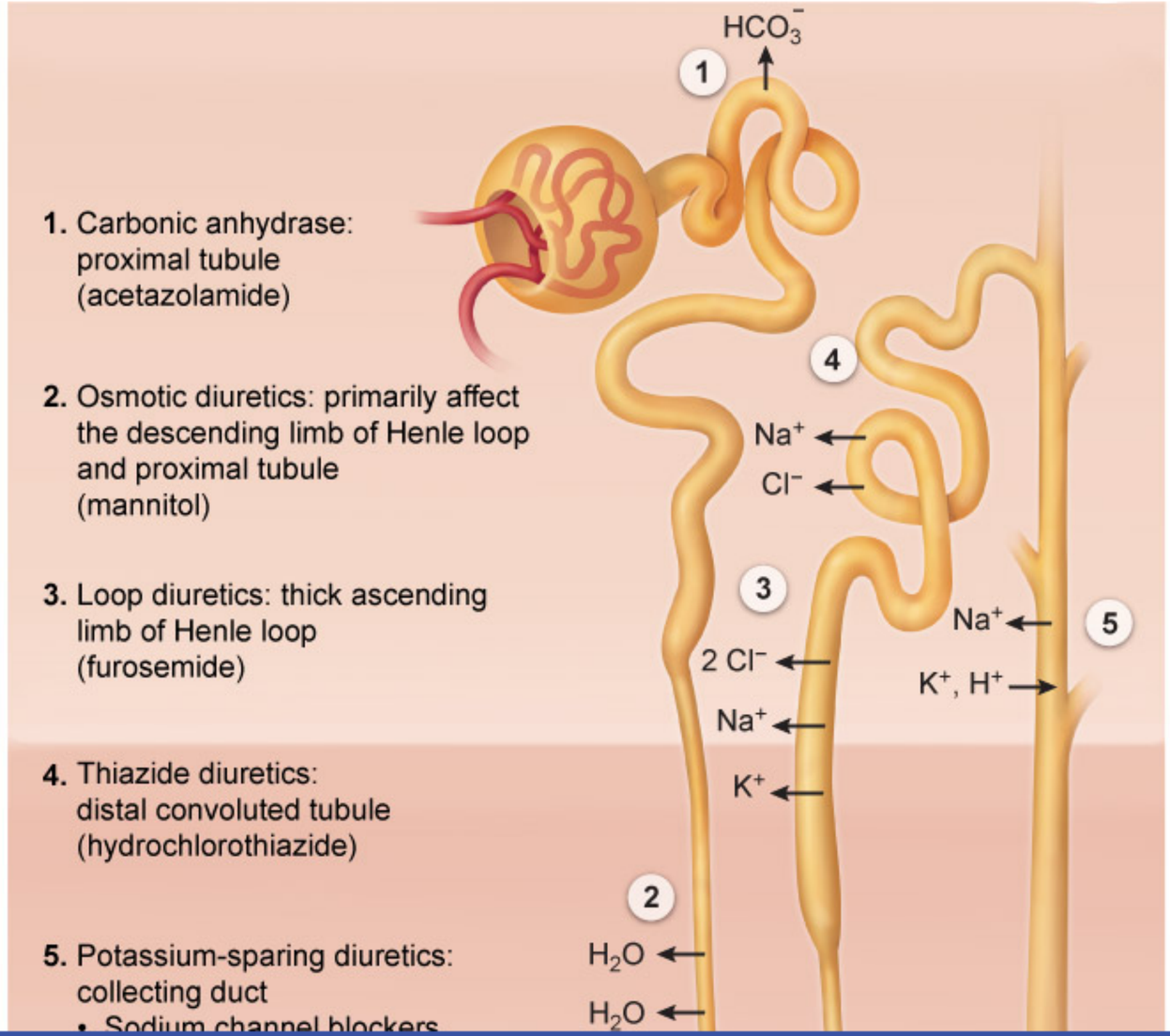
Site of inhibition for various diuretics



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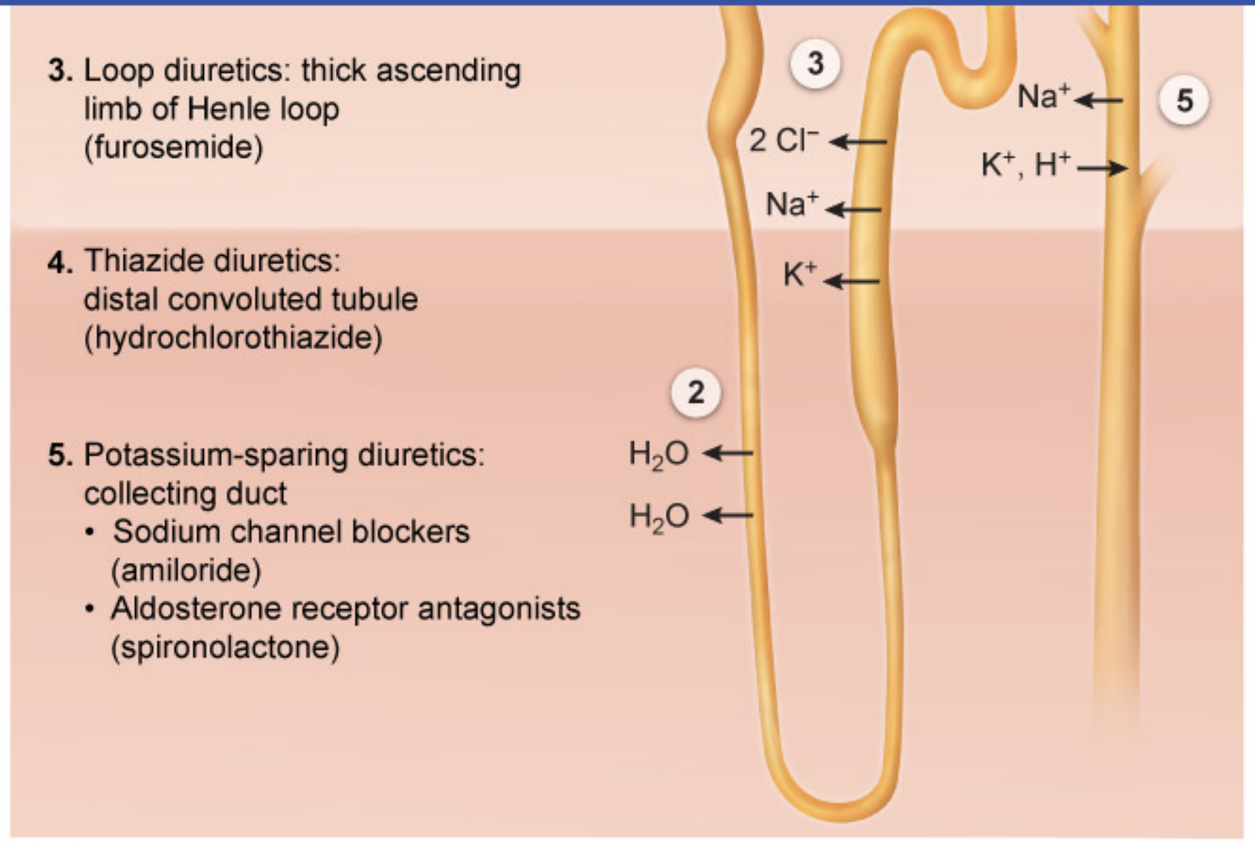

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Aldosterone is a mineralocorticoid hormone synthesized and released by the zona glomerulosa cells of the adrenal cortex. It functions as a component of the renin-aldosterone system, which is normally activated by low blood pressure and reduced renal blood flow. Under these conditions, aldosterone release is stimulated by angiotensin II. High serum potassium ion concentrations and increased ACTH levels (transient effect) can also cause aldosterone secretion.

Aldosterone increases the number of basolateral Na^+/K^+-ATPase pumps and apical sodium channels found on principal cells in the cortical collecting ducts, increasing sodium and water reabsorption. It also promotes **potassium and hydrogen ion secretion** from the principal and intercalated cells of the collecting tubules, respectively. **Aldosterone receptor antagonists** (eg, spironolactone, eplerenone) inhibit the effects of

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(Choice A) Carbonic anhydrase within proximal tubule cells synthesizes H^+, which is then secreted into tubular fluid and used by brush border carbonic anhydrase to help resorb filtered HCO_3^-. Carbonic anhydrase inhibitors such as acetazolamide inhibit both membrane-bound and cytoplasmic forms of this enzyme.

(Choice C) The $Na^+/K^+/2Cl^-$ cotransporter in the thick ascending limb is the target of loop diuretics (eg, furosemide, ethacrynic acid). These potent diuretics cause brisk diuresis by inhibiting solute reabsorption, which prevents the formation of a concentrated medullary gradient.

(Choice D) The brush border of the proximal convoluted tubule is responsible for reabsorbing two-thirds of the sodium and water filtered by the glomerulus. Transport proteins found in the brush border reabsorb filtered glucose, amino acids, phosphate, and lactate via cotransport with sodium.

(Choice E) Vasopressin (antidiuretic hormone) increases urea reabsorption in the medullary collecting tubules by increasing the number of cell surface urea transporters. This helps to strengthen the corticomedullary interstitial osmotic gradient and is necessary to produce maximally concentrated urine.

Educational objective:
Aldosterone is a component of the renin-angiotensin-aldosterone system that acts on the principal and intercalated cells of the renal collecting tubules to cause resorption of sodium and water and loss of potassium and hydrogen ions. Aldosterone receptor antagonists (eg, spironolactone, eplerenone) inhibit these effects.

Pharmacology | Renal, Urinary Systems & Electrolytes | Aldosterone antagonists

A 35-year-old woman who is being treated for bipolar disorder complains of excessive thirst and frequent urination. She awakens 3-4 times nightly to void. A urinalysis performed after 8 hours of nothing to eat or drink shows the following:

Specific gravity	1.005 (normal: 1.003-1.030)
Glucose	Negative
Protein	Negative
Ketones	Trace

Which of the following parts of the nephron is most likely impaired in this patient?

- A. A
- B. B
- C. C
- D. D
- E. E
- F. F

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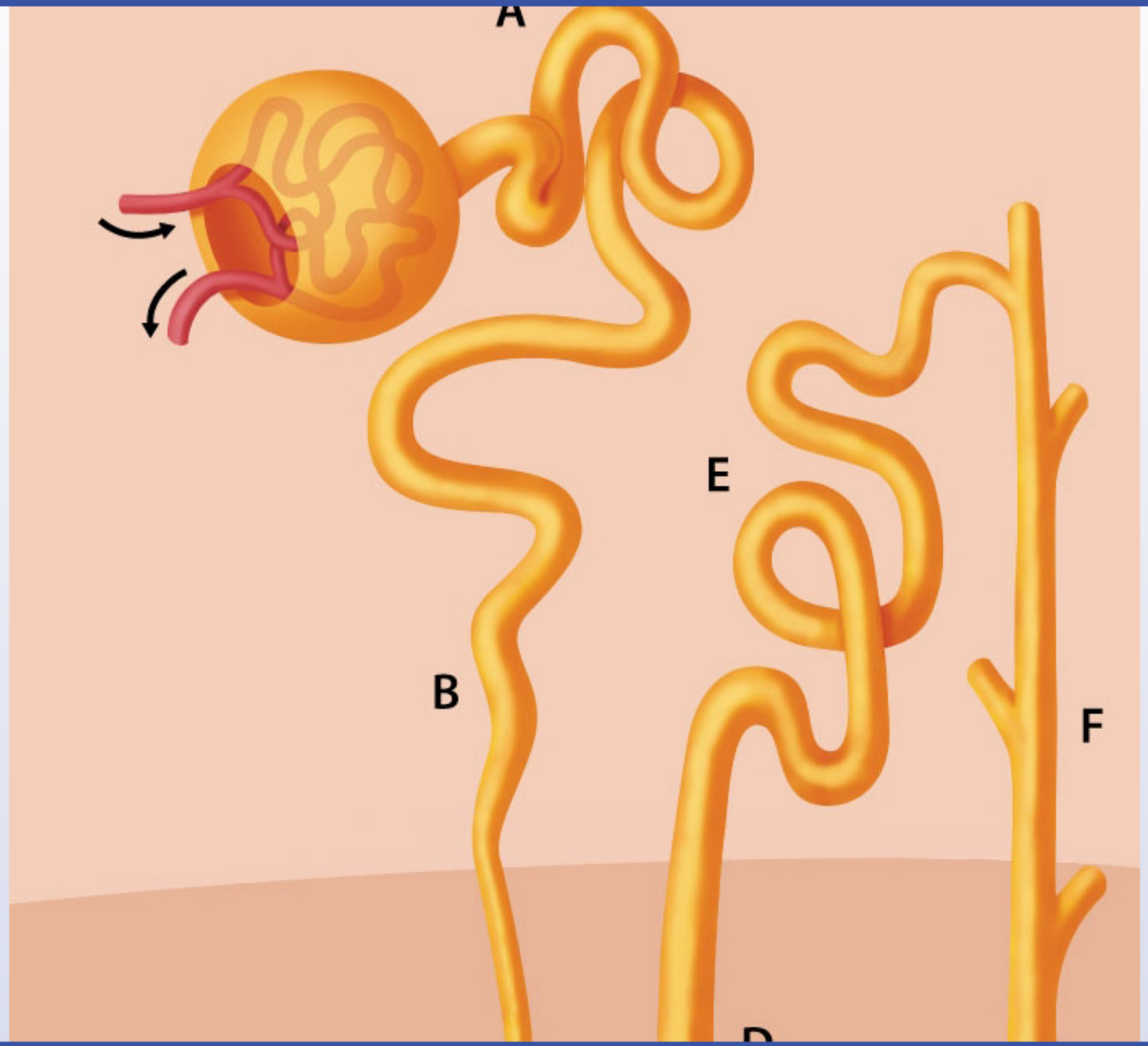
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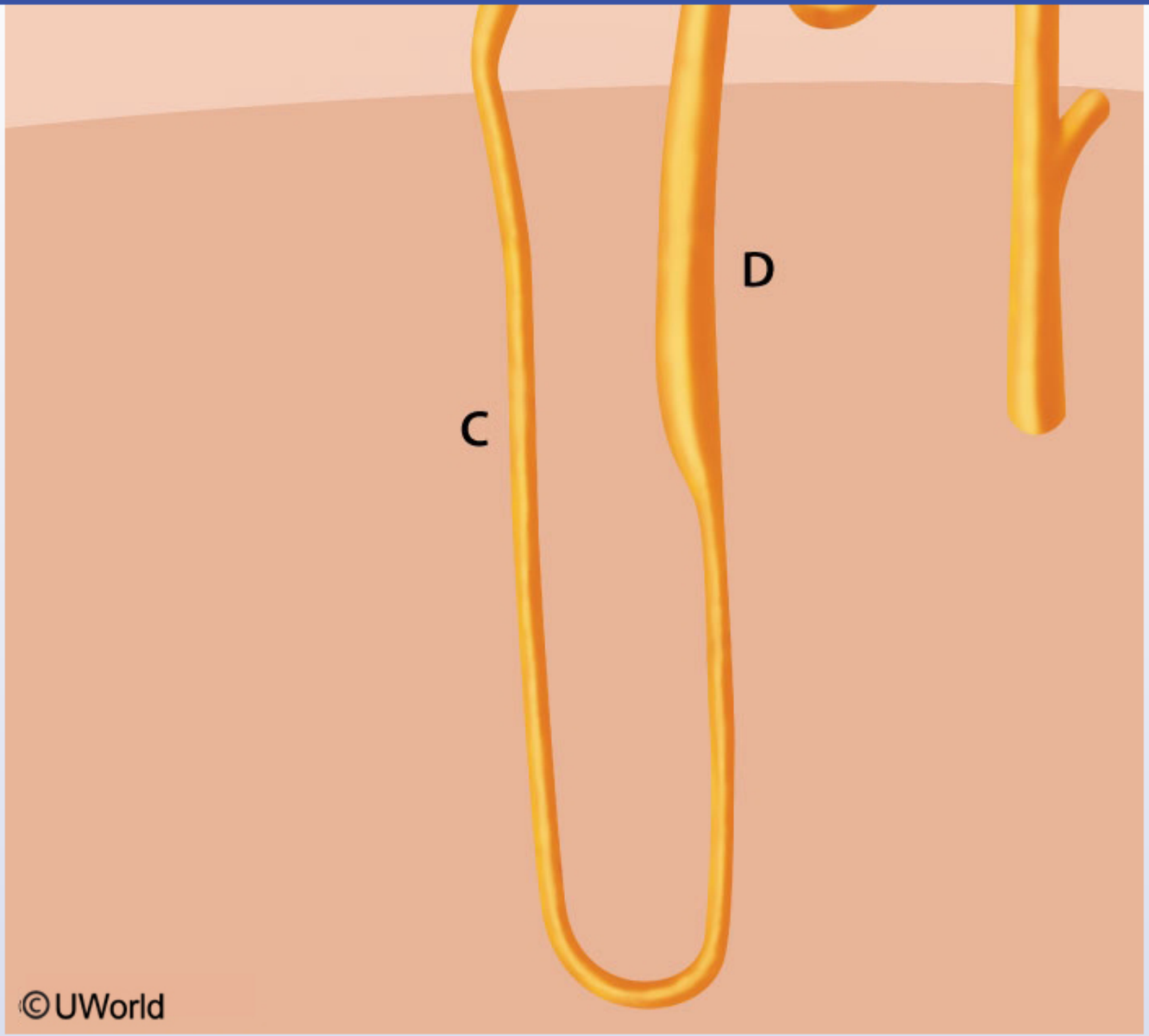

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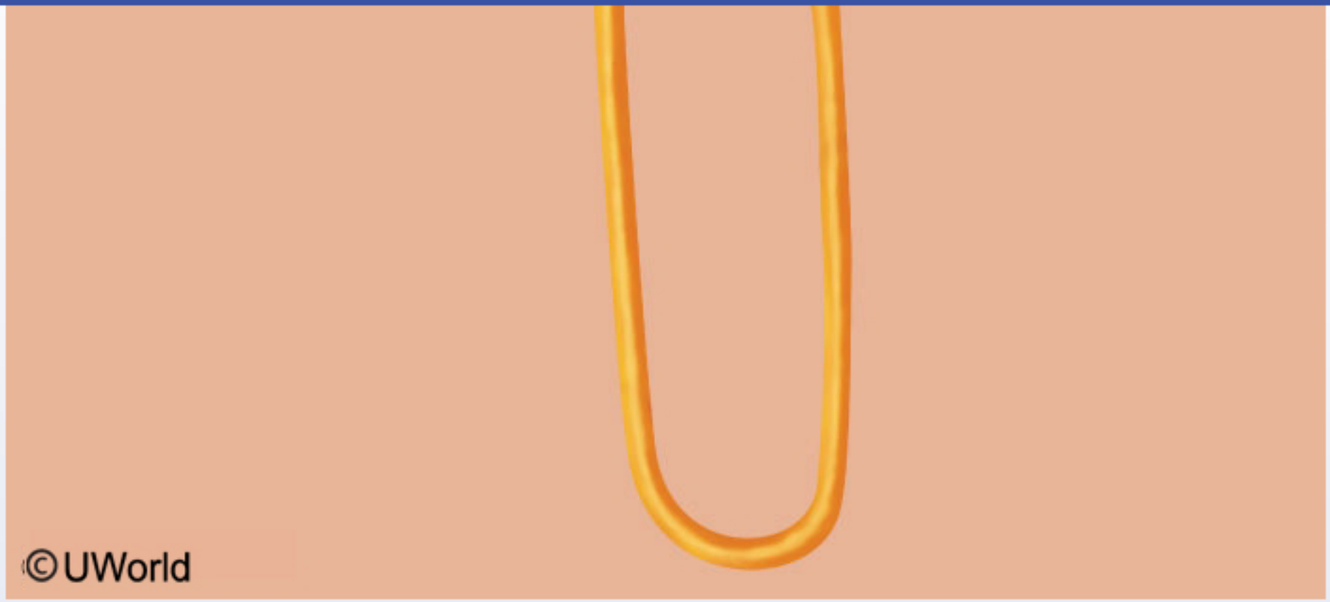

A. A

B. B

C. C

D. D

E. E

F. F

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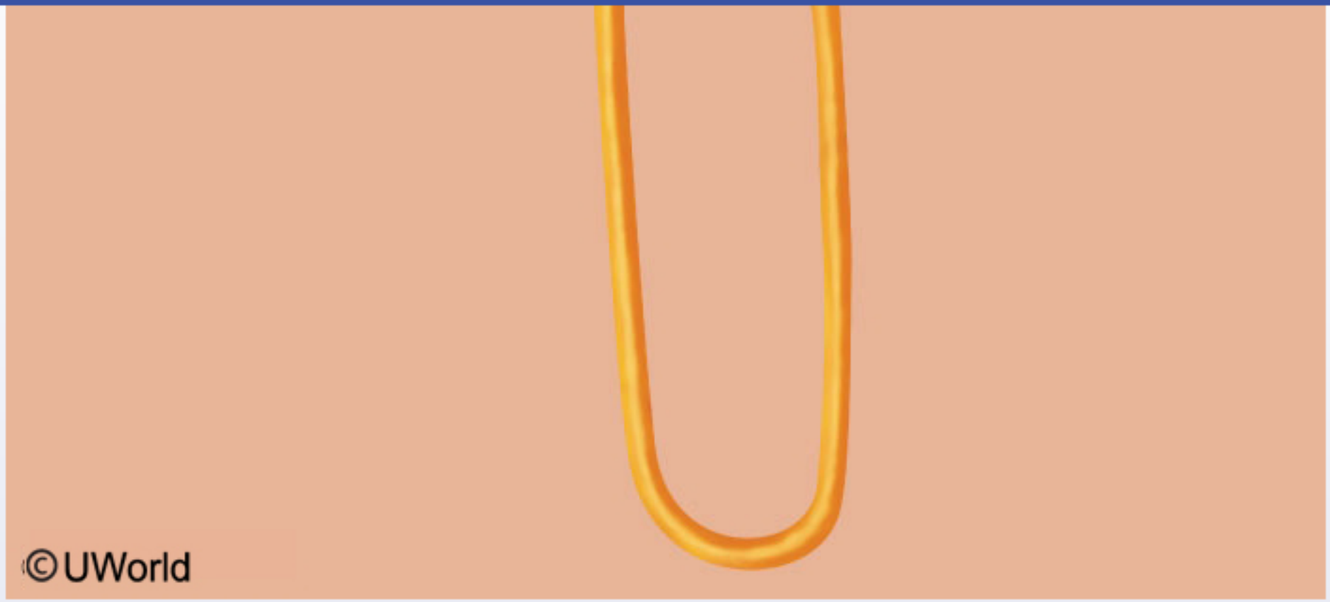

A. A (10%)

B. B (1%)

C. C (2%)

D. D (2%)

E. E (7%)

✓ F. F (75%)

Omitted
Correct answer

75%
Answered correctly

11 secs
Time Spent

04/08/2020
Last Updated

F

Explanation

This patient presents with polydipsia, polyuria, and an inappropriately **low urine specific gravity** after 8 hours of water restriction. Although within the normal range, specific gravity should be higher after water deprivation (ie, > 1.010), reflecting concentrated urine.

Given her **psychiatric history**, these findings are highly suggestive of lithium-induced nephrogenic **diabetes insipidus**. Therapy with **lithium** reduces the ability of the kidneys to concentrate urine primarily by **antagonizing the action of vasopressin** (antidiuretic hormone) in the **collecting tubules and ducts**. Nephrogenic diabetes insipidus caused by lithium usually resolves following discontinuation of the drug. However, impairment can be permanent following years of chronic use.

(Choice A) The proximal tubule is the site of action of carbonic anhydrase inhibitors.

(Choices B and C) Osmotic diuretics such as mannitol function mainly in the proximal tubule and the descending limb of the loop of Henle.

(Choice D) The thick ascending limb of the loop of Henle is the site of action of loop diuretics such as furosemide.

(Choice E) The early distal convoluted tubule is the site of action of thiazide diuretics.

Educational objective:
Lithium-induced diabetes insipidus is the result of lithium's antagonizing effect on the action of vasopressin on principal cells within the collecting duct system.

References

- Lithium: a versatile tool for understanding renal physiology.

Pharmacology	Renal, Urinary Systems & Electrolytes	Lithium
Subject	System	Topic

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A 56-year-old man with type 2 diabetes mellitus, hypertension, and chronic kidney disease is found to have a persistently elevated serum potassium level. He takes lisinopril. Blood pressure is 130/90 mm Hg. Physical examination shows no abnormalities. The patient is prescribed patiromer therapy. Which of the following best describes the mechanism of action of this medication?

A. Activates the Na^+-K^+-ATPase pump in skeletal muscle

B. Antagonizes aldosterone effect on renal tubules

C. Antagonizes membrane effects of hyperkalemia

D. Exchanges calcium for potassium in the intestine

E. Increases renal excretion of potassium

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- A. Activates the Na^+-K^+-ATPase pump in skeletal muscle (4%)
- B. Antagonizes aldosterone effect on renal tubules (6%)
- C. Antagonizes membrane effects of hyperkalemia (10%)
- ✓ D. Exchanges calcium for potassium in the intestine (40%)
- E. Increases renal excretion of potassium (37%)

Omitted
Correct answer
D

40%
Answered correctly

04 secs
Time Spent

06/04/2020
Last Updated

Explanation

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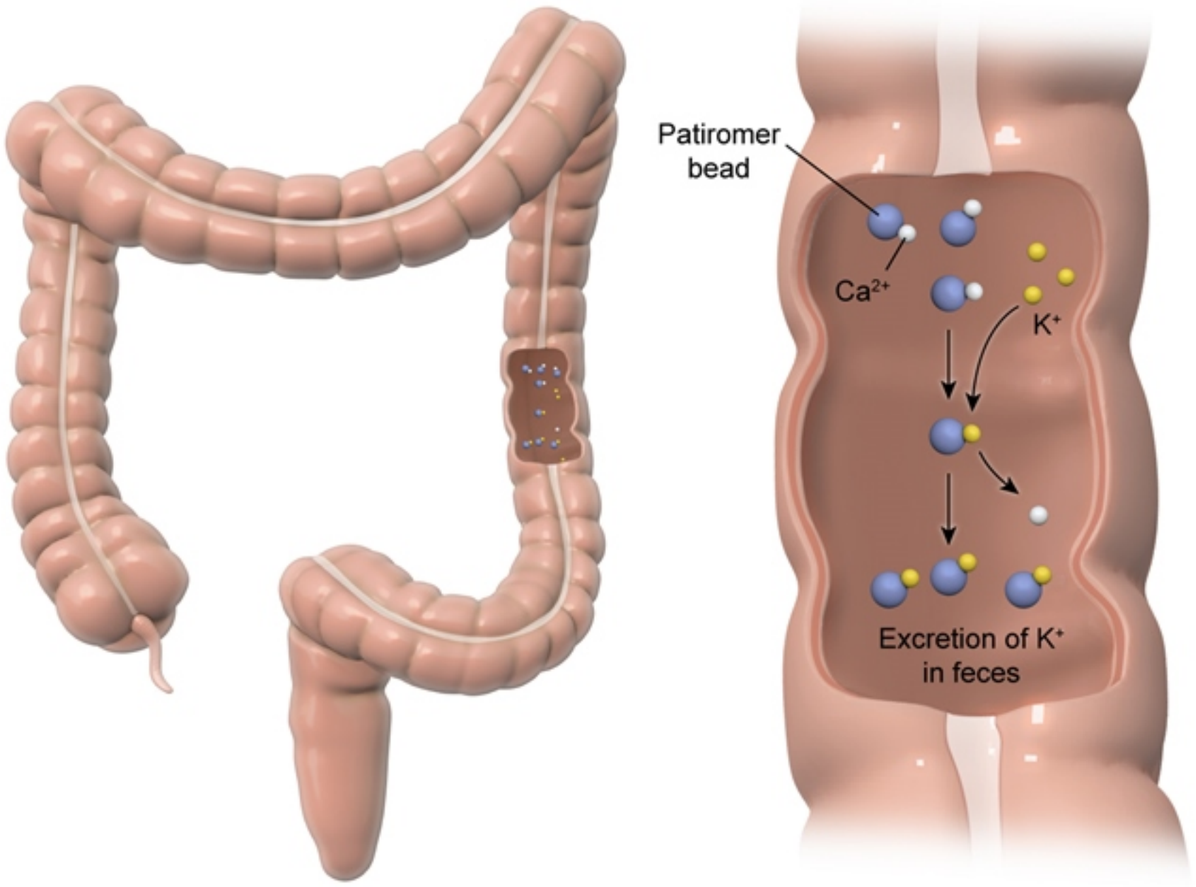
Patiromer mechanism of action



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Hyperkalemia is a common complication of chronic kidney disease that results from impaired potassium excretion. Medications that inhibit the renin-angiotensin-aldosterone system (eg, ACE inhibitors, mineralocorticoid blockers) can also worsen hyperkalemia, often limiting their use in this population.

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Patiromer is a nonabsorbable cation exchange resin that **binds colonic potassium** in **exchange for calcium**, trapping potassium within the resin where it is then excreted in the feces. It is often used for treatment of chronic hyperkalemia. However, onset of action takes several hours, so it is not recommended as monotherapy in acute hyperkalemia. Adverse effects include gastrointestinal disturbance (eg, diarrhea), hypokalemia, hypercalcemia (due to luminal exchange of calcium), and hypomagnesemia (due to off-target binding of other positive ions). Patiromer may also bind certain medications (eg, ciprofloxacin, levothyroxine).

Sodium zirconium cyclosilicate is another nonabsorbable cation exchange resin that binds intestinal potassium in exchange for sodium and hydrogen. It is more selective for potassium and does not interfere with absorption of magnesium or other medications. However, the increased sodium load may be problematic for patients sensitive to exogenous sodium (eg, cirrhosis, congestive heart failure).

(Choice A) Beta-2 agonists and insulin increase the activity of the Na^+-K^+-ATPase in skeletal muscles, which transiently increases intracellular translocation of potassium. These medications are used in the treatment of acute, severe hyperkalemia but do not have a sustained potassium-lowering effect.

(Choice B) Mineralocorticoid blockers (eg, spironolactone, eplerenone) antagonize the effects of aldosterone in the renal tubules. This leads to increased reabsorption of potassium, which will worsen hyperkalemia.

(Choice C) Calcium gluconate antagonizes the effects of hyperkalemia on cell membrane potential and is used in severe hyperkalemia to stabilize cardiac myocytes and prevent arrhythmias. It does not lower serum potassium levels.

(Choice E) Loop diuretics (eg, furosemide) increase renal excretion of potassium. Patiromer inhibits dietary potassium absorption and therefore decreases the total amount of renally excreted potassium.

Educational objective:
Patiromer is a nonabsorbable cation exchange resin used to treat hyperkalemia. It binds colonic potassium in exchange for calcium, trapping potassium within the resin where it is then excreted in the feces. Adverse effects include diarrhea, hypokalemia, hypercalcemia, and hypomagnesemia.

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Pharmacology	Renal, Urinary Systems & Electrolytes	Hyperkalemia
Subject	System	Topic

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An unresponsive 62-year-old man is brought to the emergency department after sustaining multiple injuries in a major motor vehicle accident. He is obtunded but responds to painful stimuli. His blood pressure is 160/90 mm Hg, pulse is 72/min, and respirations are 10/min. A few hours after initial treatment and stabilization, he develops severe tachypnea and decreased oxygenation. His chest x-ray shows evidence of pulmonary edema. He is rapidly intubated and given oxygen but acutely worsens and dies a few hours later, despite aggressive measures. Which of the following drugs could have caused this patient's condition?

A. Chlorthalidone
B. Bumetanide
C. Spironolactone
D. Triamterene
E. Mannitol

Submit

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A. Chlorthalidone (11%)
B. Bumetanide (17%)
C. Spironolactone (8%)
D. Triamterene (8%)
✓ E. Mannitol (54%)

Omitted
Correct answer
E

54%
Answered correctly

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Time Spent

03/23/2020
Last Updated

Explanation

This patient presents after trauma and was likely treated with mannitol, an osmotic diuretic often used in the management of cerebral edema and increased intracranial pressure. Mannitol works by rapidly increasing plasma or tubular fluid osmolality, which causes water to move from the interstitial space into the vascular space or tubular lumen. In the kidneys, osmotic diuretics primarily work in the proximal tubule and the loop of Henle to produce diuresis. In the brain, water redistribution from the tissues into the plasma helps to reduce cerebral edema and intracranial pressure. Common side effects of osmotic diuretics include headache, nausea, and vomiting. Overaggressive treatment with osmotic diuretics

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One of the more severe toxicities of aggressive osmotic diuretic therapy is pulmonary edema, caused by the rapid rise in volume that can also increase the overall hydrostatic pressure in the vasculature. The continued rise in plasma osmolality causes more water and potassium to move out of the cells and brain. This leads to further volume expansion (and possibly worsening pulmonary edema), dilutional hyponatremia and metabolic acidosis, and hyperkalemia. Therefore, osmotic diuretics should be cautiously used in high-risk patients, such as those with congestive heart failure (CHF) or preexisting pulmonary edema.

(Choice A) Thiazide diuretics are used to treat edema secondary to heart failure, renal disease, and liver disease. Common side effects include hypokalemia and hypomagnesemia. Less common side effects include hypotension, volume depletion, hypercalcemia, and hyponatremia.

(Choice B) Bumetanide is a loop diuretic that works by inhibiting NaK2Cl symporters in the ascending limb of the loop of Henle to block Na and Cl transport and increase Na, Cl, and fluid excretion. Loop diuretics are commonly used to treat pulmonary edema, venous and pulmonary congestion secondary to CHF, and peripheral edema. Common side effects include hypokalemia, hypomagnesemia, and hypocalcemia.

(Choice C) Spironolactone is an aldosterone antagonist with mild diuretic effects. It has a potassium-sparing effect and some endocrine effects and can cause significant hyperkalemia, gynecomastia, decreased libido, and erectile dysfunction.

(Choice D) Triamterene is a potassium-sparing diuretic that works by blocking sodium channels in the distal tubule and collecting duct, leading to increased sodium and fluid excretion.

Educational objective:
Mannitol is an osmotic diuretic that works by increasing plasma or tubular fluid osmolality. Increased plasma and fluid osmolality causes extraction of water from the interstitial space into the vascular space or tubular lumen, with subsequent diuresis. In the brain, water redistribution from the tissues into the plasma helps reduce edema and intracranial pressure in the setting of cerebral edema. One of the more severe toxicities of aggressive osmotic diuretics is pulmonary edema.

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Mannitol is an osmotic diuretic that works by increasing plasma or tubular fluid osmolality. Increased plasma and fluid osmolality causes extraction of water from the interstitial space into the vascular space or tubular lumen, with subsequent diuresis. In the brain, water redistribution from the tissues into the plasma helps reduce edema and intracranial pressure in the setting of cerebral edema. One of the more severe toxicities of aggressive osmotic diuretics is pulmonary edema.

References

- Mannitol revisited

Pharmacology	Renal, Urinary Systems & Electrolytes	Mannitol
Subject	System	Topic

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A 72-year-old woman presents with difficulty hearing. She was admitted 1 week ago for dyspnea, orthopnea, and bilateral leg swelling which has been slowly improving with treatment. Her family members report that for the past 2 days, she has been turning her TV volume higher and they have to speak loudly for her to hear. Her hearing was normal prior to the hospitalization. Her medical problems include hypertension, heart failure, and chronic kidney disease. Examination shows moderate bilateral sensorineural hearing loss. Which of the following medications most likely contributed to this patient's hearing impairment?

- A. Carvedilol
- B. Digoxin
- C. Furosemide
- D. Hydrochlorothiazide
- E. Ramipril
- F. Spironolactone

Submit

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A. Carvedilol (2%)
B. Digoxin (12%)
✓ C. Furosemide (70%)
D. Hydrochlorothiazide (6%)
E. Ramipril (3%)
F. Spironolactone (3%)

Omitted
Correct answer
C

70%
Answered correctly

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Time Spent

04/20/2020
Last Updated

Explanation

This patient with pulmonary and peripheral edema due to heart failure and chronic kidney disease (CKD) was likely treated with diuretics during her hospitalization. **Loop diuretics** (eg, furosemide, torsemide, bumetanide), the most commonly used first line agents, work by **inhibiting Na/K/2Cl symporters** in the ascending limb of the loop of Henle. Inhibition of similar symporters in the inner ear is believed to cause **ototoxicity** (tinnitus, vertigo, hearing impairment, or deafness). It usually occurs with higher dosages, preexisting CKD, rapid intravenous administration, or

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(Choice A) Carvedilol is a beta blocker with alpha blocking activity. Beta blockers are not initiated during decompensated heart failure as cardiac output is dependent on sympathetic input in this state. Major side effects include bradycardia, hypoglycemia, and fatigue.

(Choice B) Digoxin is used in certain patients with heart failure due to systolic dysfunction to help improve symptoms. Toxicity can cause cardiac arrhythmias, hyperkalemia, nausea, vomiting and confusion.

(Choice D) Hydrochlorothiazide is most often used for treating hypertension. Side effects of HCTZ include hypokalemia, hyponatremia and hypomagnesemia, and hypercalcemia.

(Choice E) Ramipril is an angiotensin converting enzyme inhibitor that is used in the treatment of hypertension and is beneficial in patients with heart failure. Side effects include cough, hyperkalemia and, less frequently, angioedema and anaphylactoid reactions.

(Choice F) Spironolactone works by antagonizing the effects of aldosterone in the distal tubule and collecting duct. Common side effects include hyperkalemia, gynecomastia, impotence, and decreased libido.

Educational objective:
Ototoxicity secondary to loop diuretics usually occurs with higher dosages, pre-existing chronic renal disease, rapid intravenous administration, or when used in combination with other ototoxic agents (aminoglycosides, salicylates, and cisplatin). Hearing impairment is usually reversible but may be permanent in some cases.

References

- Systemic ototoxicity: a review.

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(tinnitus, vertigo, hearing impairment, or deafness). It usually occurs with higher dosages, preexisting CKD, rapid intravenous administration, or when used in combination with other ototoxic agents (aminoglycosides, salicylates, cisplatin). Symptoms are usually reversible but hearing impairment may be permanent in some cases. Additional side effects of loop diuretics include hypokalemia, hypomagnesemia, and hypocalcemia.

(Choice A) Carvedilol is a beta blocker with alpha blocking activity. Beta blockers are not initiated during decompensated heart failure as cardiac output is dependent on sympathetic input in this state. Major side effects include bradycardia, hypoglycemia, and fatigue.

(Choice B) Digoxin is used in certain patients with heart failure due to systolic dysfunction to help improve symptoms. Toxicity can cause cardiac arrhythmias, hyperkalemia, nausea, vomiting and confusion.

(Choice D) Hydrochlorothiazide is most often used for treating hypertension. Side effects of HCTZ include hypokalemia, hyponatremia and hypomagnesemia, and hypercalcemia.

(Choice E) Ramipril is an angiotensin converting enzyme inhibitor that is used in the treatment of hypertension and is beneficial in patients with heart failure. Side effects include cough, hyperkalemia and, less frequently, angioedema and anaphylactoid reactions.

(Choice F) Spironolactone works by antagonizing the effects of aldosterone in the distal tubule and collecting duct. Common side effects include hyperkalemia, gynecomastia, impotence, and decreased libido.

Educational objective:
Ototoxicity secondary to loop diuretics usually occurs with higher dosages, pre-existing chronic renal disease, rapid intravenous administration, or when used in combination with other ototoxic agents (aminoglycosides, salicylates, and cisplatin). Hearing impairment is usually reversible but may be permanent in some cases.

References

- Systemic ototoxicity: a review.

Pharmacology	Renal, Urinary Systems & Electrolytes	Loop diuretics
Subject	System	Topic

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A previously healthy 45-year-old male undergoes an elective hernia repair under spinal anesthesia. Postoperatively, he complains of difficulty voiding. Bladder catheterization shows a post-void residual of 300cc of urine. This patient would most likely benefit from which of the following medications?

A. Finasteride
B. Phenylephrine
C. Bethanechol
D. Oxybutynin
E. Imipramine

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A previously healthy 45-year-old male undergoes an elective hernia repair under spinal anesthesia. Postoperatively, he complains of difficulty voiding. Bladder catheterization shows a post-void residual of 300cc of urine. This patient would most likely benefit from which of the following medications?

A. Finasteride (8%)
B. Phenylephrine (4%)
C. Bethanechol (75%)
D. Oxybutynin (8%)
E. Imipramine (3%)

Omitted
Correct answer
C

75%
Answered correctly

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02/03/2020
Last Updated

Explanation

This patient most likely has postoperative urinary retention, which occurs in up to 25% of patients after lower abdominal surgery. A normal post-void residual urine volume in the bladder is less than 50cc. Anesthesia and analgesia contribute to all of the following: over-distention of the bladder, a decreased micturition reflex, decreased contractility of the bladder detrusor muscle, and incomplete emptying.

Contraction of the detrusor muscle is stimulated by muscarinic cholinergic agonists. Bethanechol, a muscarinic agonist, often improves bladder-emptying in patients with post-surgery urinary retention.

(Choice A) Finasteride is prescribed for patients with bladder outlet obstruction secondary to prostatic hypertrophy. Finasteride is a 5α-reductase

Explanation

This patient most likely has postoperative urinary retention, which occurs in up to 25% of patients after lower abdominal surgery. A normal post-void residual urine volume in the bladder is less than 50cc. Anesthesia and analgesia contribute to all of the following: over-distention of the bladder, a decreased micturition reflex, decreased contractility of the bladder detrusor muscle, and incomplete emptying.

Contraction of the detrusor muscle is stimulated by muscarinic cholinergic agonists. Bethanechol, a muscarinic agonist, often improves bladder-emptying in patients with post-surgery urinary retention.

(Choice A) Finasteride is prescribed for patients with bladder outlet obstruction secondary to prostatic hypertrophy. Finasteride is a 5α-reductase inhibitor that decreases the local conversion of testosterone to dihydrotestosterone in the prostate, thereby promoting shrinkage of the gland over 6 to 12 months. Since this patient's incomplete bladder emptying is due to weak detrusor muscle contraction rather than prostatic hypertrophy, finasteride would not be likely to improve his acute condition.

(Choice B) Phenylephrine is an alpha-agonist with some selectivity for α1 receptors. The occupation of α1 receptors in the bladder actually encourages the trigone and sphincter to contract. Phenylephrine promotes, rather than alleviates, urinary retention.

(Choice D) Oxybutynin is an antimuscarinic agent commonly used for urge incontinence. If given, it will worsen this patient's condition.

(Choice E) Imipramine has anticholinergic activity, and would thus worsen this patient's condition!

Educational Objective:
Postoperative urinary retention, with incomplete bladder emptying, is a common complication thought to involve decreased micturition reflex activity, decreased contractility of the bladder detrusor, and/or increased vesical sphincter tone. This condition may be treated with a muscarinic agonist (bethanechol) or an α1 blocking drug.

Pharmacology	Renal, Urinary Systems & Electrolytes	Urinary retention
Subject	System	Topic

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A 24-year-old woman with a medical history of bronchial asthma comes to the office due to shortness of breath and wheezing for the past 2-3 days. She developed a cold 4 days ago and is not feeling well. The patient has a nebulizer at home and used multiple doses of albuterol with little response prior to arriving. She takes no other medications. The patient is diaphoretic and in moderate respiratory distress. Respiratory examination shows bilateral wheezing, diffusely decreased breath sounds, and increased use of accessory muscles of respiration. Laboratory results reveal a serum potassium of 3 mEq/L. Which of the following mechanisms is the most likely cause of this patient's hypokalemia?

A. Decreased oral intake of potassium

B. Development of respiratory acidosis

C. Increased sweat loss of potassium

D. Increased urinary excretion of potassium

E. Intracellular shift of potassium

Submit

A 24-year-old woman with a medical history of bronchial asthma comes to the office due to shortness of breath and wheezing for the past 2-3 days. She developed a cold 4 days ago and is not feeling well. The patient has a nebulizer at home and used multiple doses of albuterol with little response prior to arriving. She takes no other medications. The patient is diaphoretic and in moderate respiratory distress. Respiratory examination shows bilateral wheezing, diffusely decreased breath sounds, and increased use of accessory muscles of respiration. Laboratory results reveal a serum potassium of 3 mEq/L. Which of the following mechanisms is the most likely cause of this patient's hypokalemia?

- A. Decreased oral intake of potassium (0%)
- B. Development of respiratory acidosis (14%)
- C. Increased sweat loss of potassium (1%)
- D. Increased urinary excretion of potassium (12%)
- ✓ E. Intracellular shift of potassium (71%)

Omitted
Correct answer
E

71%
Answered correctly

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Last Updated

Explanation

Causes of hypokalemia	
Decreased intake	• Starvation, anorexia
	• Insulin (eg, treatment of DKA, refeeding syndrome) • ß-adrenergic activity

Explanation

Causes of hypokalemia	
Decreased intake	• Starvation, anorexia

Intracellular translocation	• Insulin (eg, treatment of DKA, refeeding syndrome)
	• β-adrenergic activity
	  ◦ Pharmacologic (eg, albuterol, dobutamine)
	  ◦ Stress-induced (eg, alcohol withdrawal, acute MI)
	• Alkalosis (respiratory or metabolic)
	• ↑ Cell reproduction (eg, acute myeloid leukemia, GM-CSF)

Gastrointestinal loss	• Diarrhea, vomiting, hyperaldosteronism
Urinary loss	• Hyperaldosteronism, diuretics, RTA types 1 and 2
Sweat loss	• Extreme exercise in hot climate

DKA = diabetic ketoacidosis; **MI** = myocardial infarction; **GM-CSF** = granulocyte-macrophage colony-stimulating factor; **RTA** = renal tubular acidosis.

Hypokalemia is a common medical condition that can result from several mechanisms, including decreased oral intake, renal or gastrointestinal loss, and increased entry into cells. In a patient receiving multiple doses of albuterol, the most likely etiology is **intracellular shift of potassium**.

Potassium is primarily stored intracellularly (~98% of total body stores) through the action of the **Na-K-ATPase pump**, which exchanges sodium for potassium against their concentration gradient. The large concentration difference of intracellular (~150 mEq/L) to extracellular potassium (~4 mEq/L) is a major driver of the resting membrane potential. Alterations in this ratio can impair action potential generation, explaining why patients with marked hyper- or hypokalemia can develop muscular weakness and cardiac arrhythmias.

Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous catecholamines and therapeutic beta-2 agonists (eg, **albuterol**, dobutamine) can cause **transient hypokalemia** due to increased **transport of potassium intracellularly**. Similar effects can also occur with sympathomimetics (eg, pseudoephedrine) and insulin, which also increase Na-K-ATPase activity.

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(Choice A) Decreased oral intake of potassium is a rare cause of hypokalemia. Because the kidneys can lower potassium excretion in the setting of reduced potassium intake, most patients do not develop hypokalemia unless fasting is prolonged (eg, starvation).

(Choice B) Respiratory acidosis may occur as a complication of asthma or chronic obstructive pulmonary disease due to CO_2 retention; however, acidosis causes potassium to shift to the extracellular space, leading to hyperkalemia (not hypokalemia). In contrast, alkalosis causes intracellular shift of potassium, resulting in transient hypokalemia.

(Choice C) Significant diaphoresis (eg, marathon running in a hot climate) can result in potassium depletion. However, normal sweating (as could occur in patients with increased work of breathing) would not result in significant potassium loss.

(Choice D) Increased urinary potassium loss can occur due to diuretic use or elevated aldosterone levels (eg, renovascular disease, primary hyperaldosteronism). While beta-1 agonists can result in increased renin release (leading to elevated aldosterone levels and increased renal potassium loss), beta-2 agonists (eg, albuterol) do not have a significant effect on urinary potassium excretion.

Educational objective:
Potassium is primarily stored intracellularly (~98% of total body stores) through the action of the Na-K-ATPase pump. Beta-adrenergic activity increases the activity of the Na-K-ATPase pump; therefore, both endogenous catecholamines and therapeutic beta-2 agonists (eg, albuterol, dobutamine) can cause transient hypokalemia due to increased transport of potassium intracellularly.

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Pharmacology	Renal, Urinary Systems & Electrolytes	Beta 2 agonists
Subject	System	Topic

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A 70-year-old man comes to the office for follow-up of hypertension. He has been taking amlodipine but his recent home blood pressure readings have been elevated. The patient has a long smoking history and, despite many attempts at quitting, continues to smoke cigarettes. Blood pressure is 140/90 mm Hg and pulse is 76/min. Examination shows a bruit on auscultation of the abdomen. Further evaluation reveals bilateral renal artery stenosis. After initial discussion, the patient is started on daily lisinopril therapy. The patient is advised to return to the clinic in a few days. The close follow-up is recommended due to which of the following anticipated effects in this patient's kidney function?

	Renal perfusion	Intraglomerular pressure	Filtration fraction
A.	Decreased	Decreased	Decreased
B.	Decreased	Increased	Increased
C.	Increased	Decreased	Decreased
D.	Increased	Increased	Decreased
E.	Increased	Increased	Increased

Submit

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	Renal perfusion	Intraglomerular pressure	Filtration fraction
✓ A. (37%)	Decreased	Decreased	Decreased
B. (10%)	Decreased	Increased	Increased
C. (38%)	Increased	Decreased	Decreased
D. (5%)	Increased	Increased	Decreased
E. (7%)	Increased	Increased	Increased

Omitted
Correct answer
A

37%
Answered correctly

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Explanation

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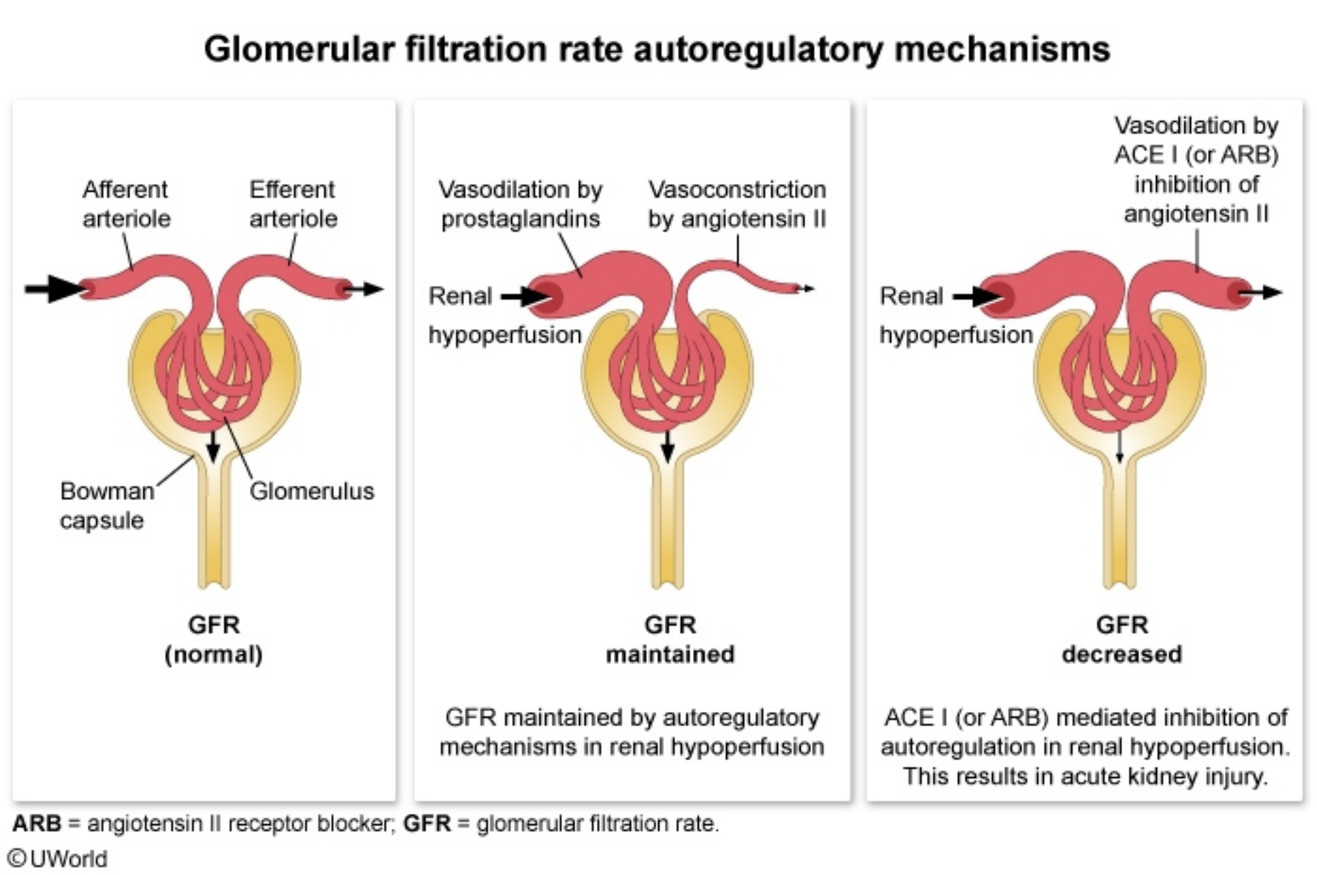
Explanation



ARB = angiotensin II receptor blocker; **GFR** = glomerular filtration rate.

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This patient has **bilateral renal artery stenosis** (RAS) and is at risk for acute renal failure with the initiation of an ACE inhibitor. Bilateral RAS, which typically occurs in older patients with widespread atherosclerosis, results in a reduction of renal perfusion. This leads to a lowered glomerular filtration rate (GFR) and activation of the renin-angiotensin-aldosterone system. **Angiotensin II**, a potent vasoconstrictor, increases systemic pressure and preferentially constricts the efferent arteriole, which increases intraglomerular hydrostatic pressure to maintain adequate GFR. The filtration fraction (FF)—the ratio of GFR to renal plasma flow (RPF) (FF = GFR/RPF)—is increased as the GFR remains relatively preserved despite the decreased RPF.

This results in acute kidney injury.

ARB = angiotensin II receptor blocker; **GFR** = glomerular filtration rate.

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ACE inhibitors (eg, lisinopril) lower angiotensin II levels, causing a reduction in systemic pressures and relative dilation of the efferent arteriole. In patients with bilateral RAS, the reduced systemic pressures are no longer high enough to overcome the stenosis, and **renal blood flow drops**. The dilation of the efferent arteriole leads to a **reduction of intraglomerular filtration pressure**, which results in the **reduction of GFR and filtration fraction**.

Although patients with bilateral RAS treated with ACE inhibitors are at risk for acute renal failure, most patients can tolerate the medication with only a mild (<30%) rise in serum creatinine. In addition, risk can be reduced with discontinuation of diuretics, as volume depletion increases the dependence on efferent arteriolar constriction to maintain GFR.

Educational objective:
Patients with bilateral renal artery stenosis have reduced renal perfusion (due to atherosclerotic blockage) and are dependent upon angiotensin II-induced efferent vasoconstriction to maintain glomerular filtration rate. ACE inhibitors block angiotensin II-mediated vasoconstriction, which can reduce systemic blood pressure and lower renal perfusion. In addition, ACE inhibitors cause dilation of the efferent arteriole, leading to a reduction in glomerular filtration rate and renal filtration fraction.

Pharmacology	Renal, Urinary Systems & Electrolytes	ACE inhibitors
Subject	System	Topic

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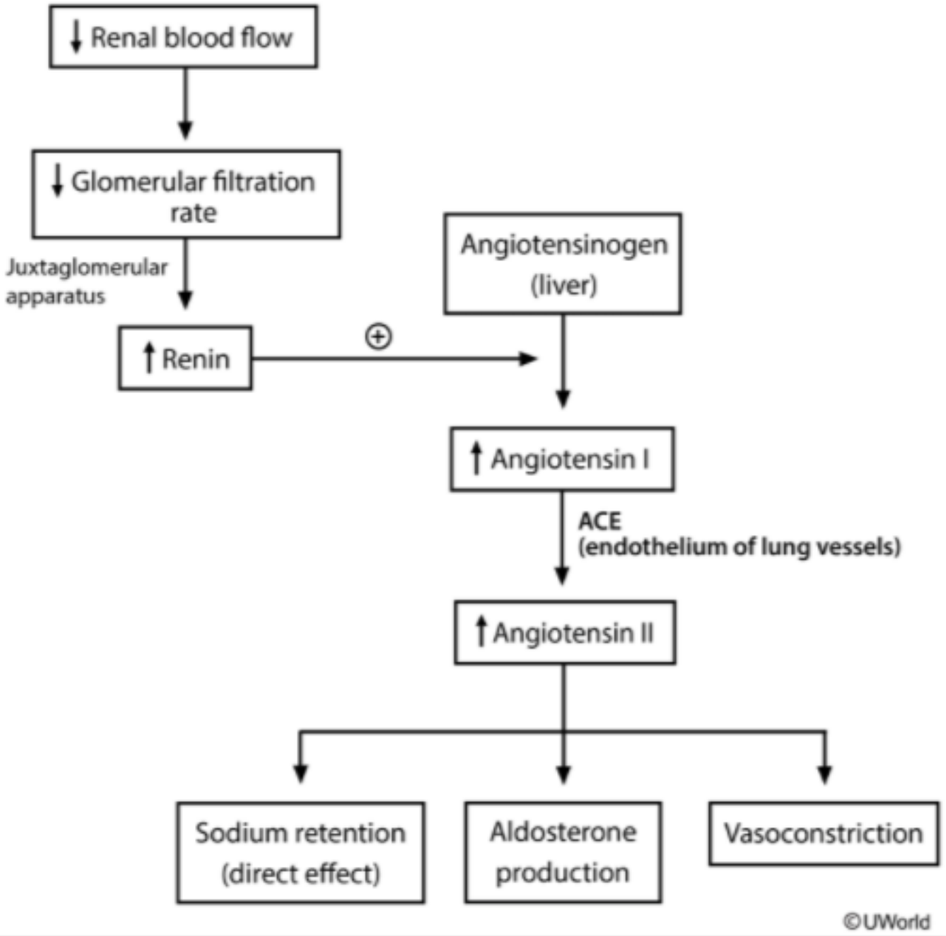
This results in acute kidney injury.

Exhibit Display

Renin-angiotensin system



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A 55-year-old woman is treated with ramipril for primary (essential) hypertension. Her blood pressure decreases to normal value over several weeks of treatment. The patient seems to be compliant with her medication and experiences no significant side effects. She has no other medical issues and takes no other medications. She does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin
A.	↑	↑	↓	↓	↑
B.	↑	↑	↑	↓	↑
C.	↑	↑	↑	↓	No change
D.	↑	↑	↓	↓	↓
E.	↑	↓	↓	↓	↓
F.	↓	↓	↓	↓	No change

Submit

A 55-year-old woman is treated with ramipril for primary (essential) hypertension. Her blood pressure decreases to normal value over several weeks of treatment. The patient seems to be compliant with her medication and experiences no significant side effects. She has no other medical issues and takes no other medications. She does not use tobacco, alcohol, or illicit drugs. Physical examination shows no abnormalities. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin
✓ A. (85%)	↑	↑	↓	↓	↑
B. (2%)	↑	↑	↑	↓	↑
C. (1%)	↑	↑	↑	↓	No change
D. (6%)	↑	↑	↓	↓	↓
E. (1%)	↑	↓	↓	↓	↓
F. (3%)	↓	↓	↓	↓	No change

Omitted
Correct answer
A

85%
Answered correctly

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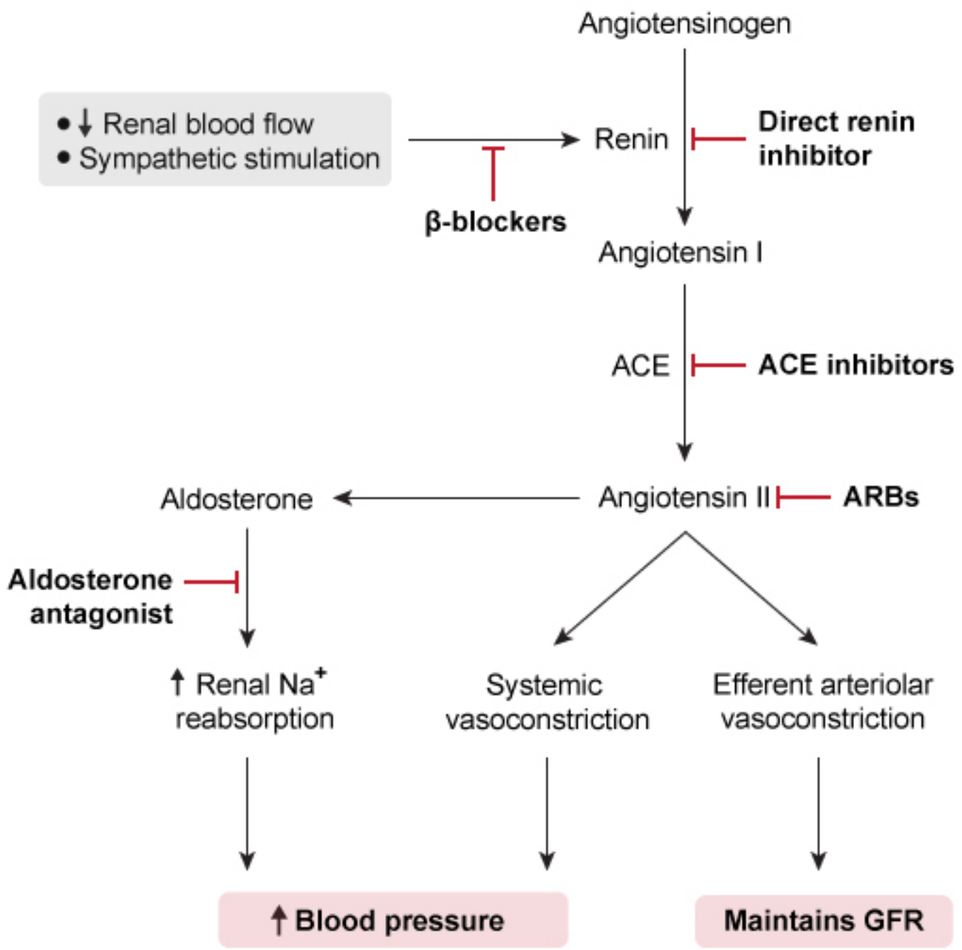
Renin-angiotensin-aldosterone system & antihypertensives



GFR = glomerular filtration rate.

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↑ Blood pressure | Maintains GFR

GFR = glomerular filtration rate.
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The renin-angiotensin-aldosterone system (RAAS) is one of the most important neurohormonal systems, regulating arterial blood pressure and sodium and fluid content in the body. In response to decreased sodium, fluid volume, or arterial blood pressure, renin is released from the kidneys, converting angiotensinogen to angiotensin I. Subsequently, angiotensin-converting enzyme (ACE) converts angiotensin I to angiotensin II. Angiotensin II then increases aldosterone secretion from the adrenal cortex, leading to increased sodium and fluid retention in the collecting tubules of the kidneys. Angiotensin II is also a potent vasoconstrictor that ultimately increases systemic vascular resistance and arterial pressure.

Angiotensin II itself is involved in 2 negative feedback mechanisms that help regulate the RAAS. In short-loop negative feedback, elevated angiotensin II stimulates the angiotensin receptors on juxtaglomerular cells to inhibit renin release. In long-loop negative feedback, increased blood pressure and sodium levels (due to angiotensin II) eventually decrease renin release via intrarenal baroreceptor and macula densa pathways, respectively.

ACE inhibitors such as ramipril block ACE and decrease the conversion of angiotensin I to angiotensin II, effectively blocking arteriolar vasoconstriction and aldosterone secretion. In addition to decreased blood pressure and sodium levels, **decreased angiotensin II** levels also interfere with negative feedback mechanisms, ultimately activating the RAAS to **promote renin release**. ACE is also responsible for the breakdown of bradykinin; therefore, ACE inhibitors lead to **increased bradykinin** levels, which are thought to cause the characteristic ACE inhibitor–induced cough.

Educational objective:
Angiotensin-converting enzyme (ACE) inhibitors block the effect of ACE, decreasing angiotensin II and aldosterone levels. By decreasing angiotensin II levels, ACE inhibitors directly interrupt negative feedback loops, thereby increasing renin and angiotensin I levels. ACE is also responsible for the breakdown of bradykinin; ACE inhibitors therefore increase bradykinin levels.

Pharmacology	Renal, Urinary Systems & Electrolytes	Renin angiotensin aldosterone system
Subject	System	Topic

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A 70-year-old man comes to the office due to increasing headaches, nausea, and vomiting. The patient has never had these symptoms before. Medical history is significant for a transient ischemic attack that led to a right carotid endarterectomy 5 years ago. He has no other medical conditions, and his only medications are aspirin and atorvastatin. The patient smoked a pack of cigarettes a day for 20 years but quit 20 years ago. Blood pressure is 220/120 mm Hg and pulse is 70/min. Neurologic examination shows no focal lesions. Bilateral abdominal bruits are present. Blood testing in this patient would most likely show which of the following?

	Renin	Aldosterone	Angiotensin II	Potassium
A.	↑	↑	↑	↑
B.	↑	↑	↑	↓
C.	↑	↑	↓	↓
D.	↑	↓	↓	↓
E.	↓	↓	↓	↓
F.	↓	↓	↓	↑
G.	↓	↓	↑	↑
H.	↓	↑	↑	↑

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	Renin	Aldosterone	Angiotensin II	Potassium
A. (5%)	↑	↑	↑	↑
✓ B. (80%)	↑	↑	↑	↓
C. (0%)	↑	↑	↓	↓
D. (0%)	↑	↓	↓	↓
E. (1%)	↓	↓	↓	↓
F. (9%)	↓	↓	↓	↑
G. (0%)	↓	↓	↑	↑
H. (0%)	↓	↑	↑	↑

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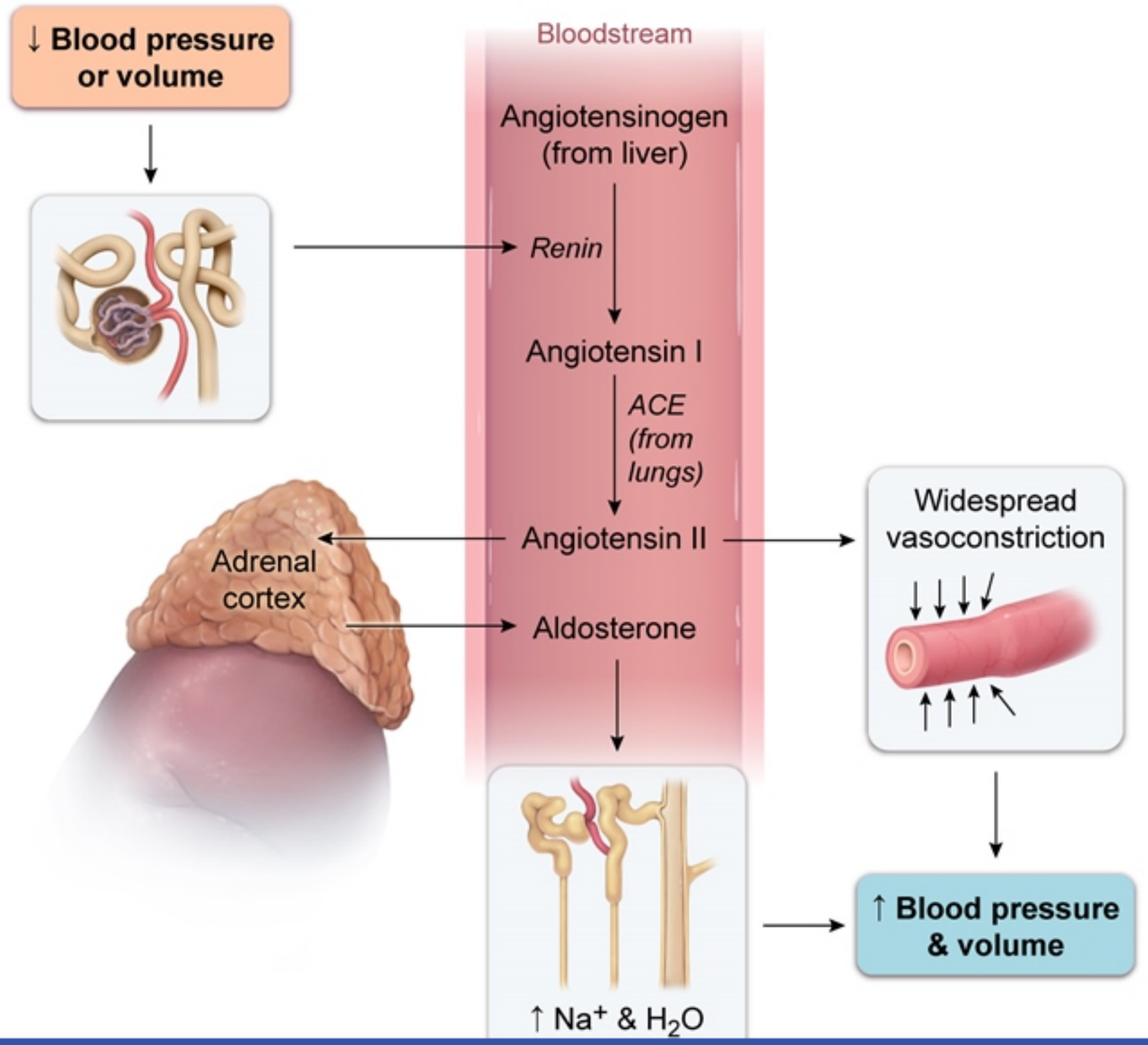
Renin-angiotensin system (RAS)



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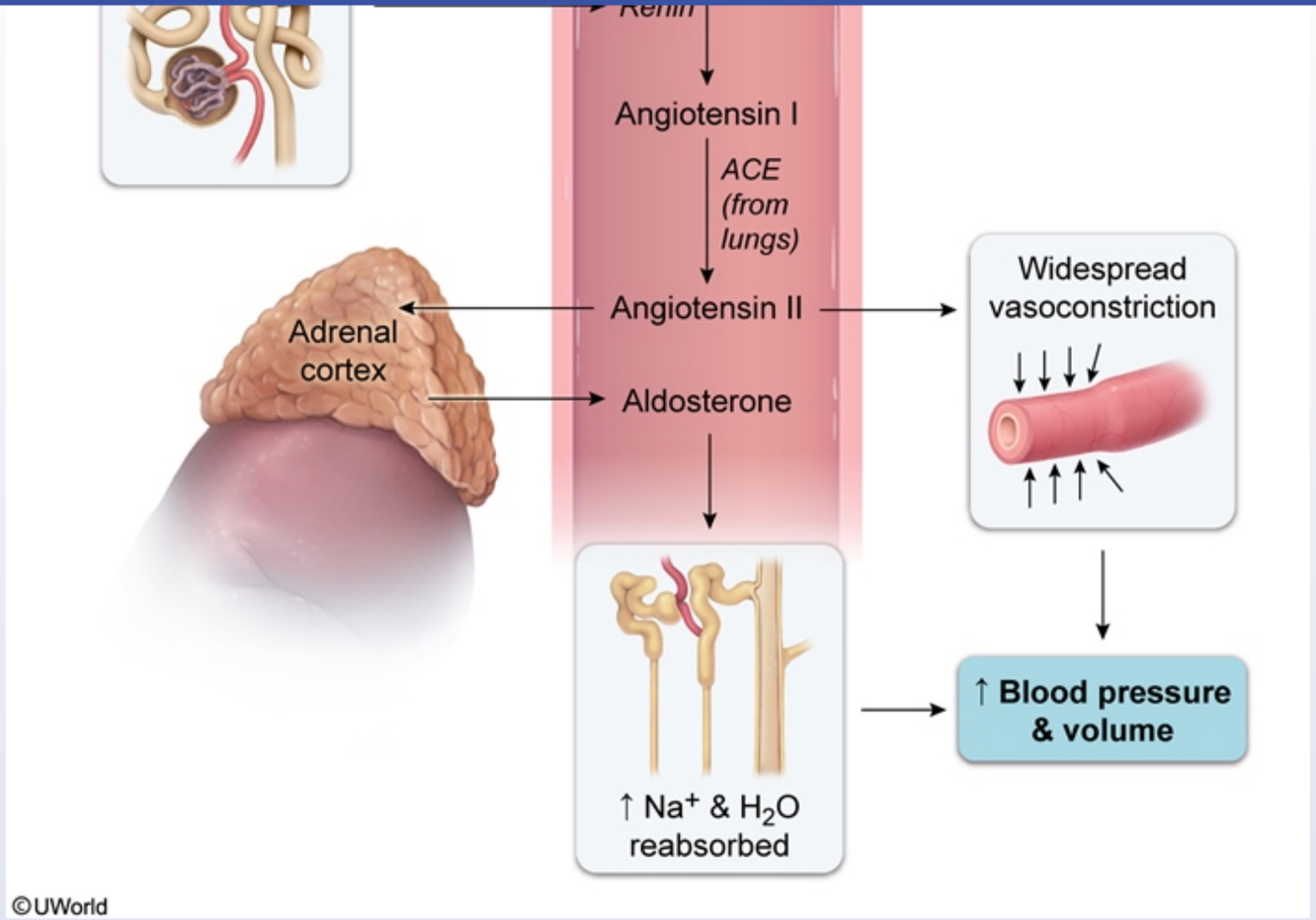
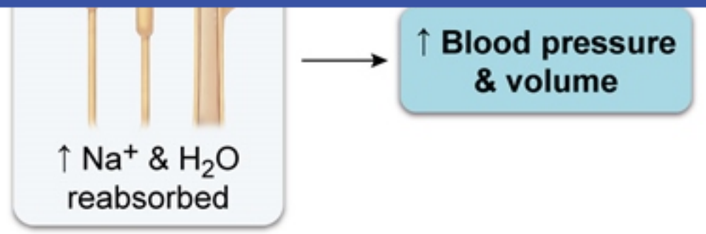


This patient has a hypertensive emergency, with markedly elevated blood pressure and symptoms (headache, vomiting) suggesting elevated intracranial pressure. In conjunction with his bilateral **abdominal bruits** (abnormal sound caused by turbulent blood flow), this presentation suggests renovascular hypertension from **bilateral renal artery stenosis** (RAS). Although RAS can be caused by a variety of lesions (eg, fibromuscular dysplasia in young women), >90% of cases are caused by atherosclerotic narrowing of the proximal renal artery. Therefore, it is most common in older patients with other atherosclerotic disease (eg, carotid stenosis, as in this patient) or risk factors (eg, diabetes, hyperlipidemia, smoking).



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This patient has a hypertensive emergency, with markedly elevated blood pressure and symptoms (headache, vomiting) suggesting elevated intracranial pressure. In conjunction with his bilateral **abdominal bruits** (abnormal sound caused by turbulent blood flow), this presentation suggests renovascular hypertension from **bilateral renal artery stenosis** (RAS). Although RAS can be caused by a variety of lesions (eg, fibromuscular dysplasia in young women), >90% of cases are caused by atherosclerotic narrowing of the proximal renal artery. Therefore, it is most common in older patients with other atherosclerotic disease (eg, carotid stenosis, as in this patient) or risk factors (eg, diabetes, hyperlipidemia, smoking).

Decreased renal artery perfusion activates the renin-angiotensin-aldosterone system. The juxtaglomerular cells increase secretion of **renin**, which converts angiotensinogen to angiotensin I. Angiotensin I is then converted to angiotensin II by angiotensin-converting enzyme. **Angiotensin II**, a potent vasoconstrictor, causes increased peripheral resistance and elevated systemic blood pressure. In addition, it stimulates the secretion of **aldosterone**, which increases renal Na^+ reabsorption and K^+ and H^+ excretion, resulting in relative **hypokalemia** and metabolic alkalosis.

Educational objective:
Renal artery stenosis (eg, severe hypertension, abdominal bruits) causes decreased renal artery perfusion, which activates the renin-angiotensin-aldosterone system. Increased secretion of renin leads to increased production of angiotensin I and angiotensin II, which causes increased peripheral resistance and elevated systemic blood pressure. Increased aldosterone secretion causes increased renal Na^+ reabsorption and K^+ and H^+ excretion, resulting in relative hypokalemia and metabolic alkalosis.

Pharmacology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis
Subject	System	Topic

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A 43-year-old previously healthy man is hospitalized after sustaining a head injury in a motor vehicle collision. Several days later, the patient develops worsening serum electrolyte disturbances. Further evaluation reveals the cause is inappropriate antidiuretic hormone secretion. Treatment with a vasopressin V2 receptor antagonist is initiated. Which of the following changes are most likely to occur as a direct result of the administered medication?

	Plasma osmolality	Urine output	Urinary sodium excretion
A.	Decrease	Decrease	No change
B.	Decrease	Increase	Increase
C.	Increase	Decrease	Decrease
D.	Increase	Increase	Increase
E.	Increase	Increase	No change

Submit

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	Plasma osmolality	Urine output	Urinary sodium excretion
A. (5%)	Decrease	Decrease	No change
B. (9%)	Decrease	Increase	Increase
C. (5%)	Increase	Decrease	Decrease
D. (16%)	Increase	Increase	Increase
✓ E. (63%)	Increase	Increase	No change

Omitted
Correct answer
E

63%
Answered correctly

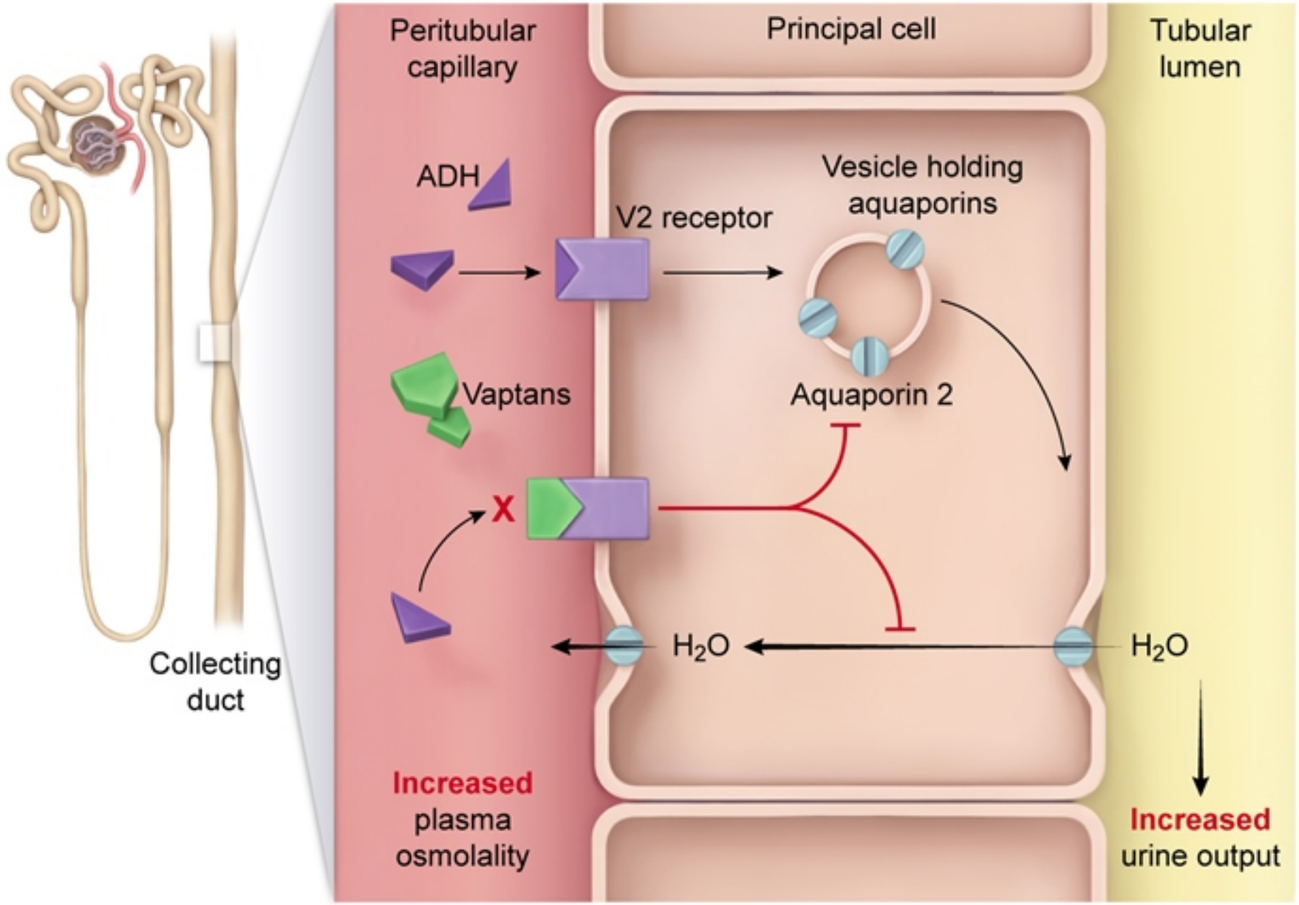
01 sec
Time Spent

05/06/2020
Last Updated

Explanation

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

Vaptan mechanism of action



Vaptans cause a selective water diuresis.

ADH = antidiuretic hormone; **V2** = vasopressin receptor 2.

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This patient developed the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**) following a head injury. Antidiuretic hormone (ie, vasopressin) is normally secreted in response to elevated plasma osmolality (eg, dehydration) or decreased arterial blood volume. It stimulates

This patient developed the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**) following a head injury. Antidiuretic hormone (ie, vasopressin) is normally secreted in response to elevated plasma osmolality (eg, dehydration) or decreased arterial blood volume. It stimulates the renal collecting ducts to reabsorb water back into the systemic circulation, which then lowers the serum osmolality and suppresses further ADH secretion. In SIADH, uncontrolled ADH secretion leads to **excessive water reabsorption**, which results in the following:

- Low plasma osmolality and **hyponatremia**
- Low urine output and high urine osmolality

Vaptans (eg, tolvaptan) are vasopressin **V2 receptor antagonists** (ie, **aquaretics**) used to treat hyponatremia. They **increase free water excretion** by blocking the antidiuretic action of ADH in the kidney and have **no direct effect on sodium or potassium excretion**. As such, vaptans produce the following alterations that help correct SIADH:

- **Increased plasma osmolality** with increased serum sodium levels
- **Increased urine output** with lower urine osmolality

(Choice A) Central diabetes insipidus is characterized by decreased ADH release, which causes increased plasma osmolality (ie, hypernatremia) and production of dilute urine; treatment with desmopressin, a vasopressin receptor-2 agonist, results in decreased plasma osmolality and urine output without directly affecting sodium excretion.

(Choice B) Thiazide diuretics inhibit the sodium-chloride cotransporter in the distal convoluted tubule, increasing renal excretion of sodium and water (associated with an increase in urine volume). Thiazides also increase water reabsorption in the inner medullary collecting duct, which can contribute to decreased plasma osmolality (ie, hyponatremia).

(Choice C) Volume contraction (eg, dehydration) results in increased plasma osmolality. The resulting activation of the renin-angiotensin-aldosterone system along with increased ADH secretion reduces urine output (due to ADH) and sodium excretion (due to aldosterone).

(Choice D) Mannitol is an osmotic diuretic that is used to treat acutely elevated intracerebral pressure (eg, intracranial hematoma). It raises plasma osmolality and inhibits water reabsorption in the renal tubules. Sodium excretion is variably increased due to solvent drag (high flow of water carries sodium through the tubules into urine).

Educational objective:
Vaptans (eg, tolvaptan) are vasopressin V2 receptor antagonists (ie, aquaretics) used to treat hyponatremia. Vaptans block the effects of

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Educational objective:
Vaptans (eg, tolvaptan) are vasopressin V2 receptor antagonists (ie, aquaretics) used to treat hyponatremia. Vaptans block the effects of antidiuretic hormone (vasopressin), increasing renal free water excretion without directly affecting excretion of sodium or potassium. Diuresis of free water with vaptans results in increased plasma osmolality, increased serum sodium, increased urine output, and lowered urine osmolality.

Pharmacology	Renal, Urinary Systems & Electrolytes	SIADH
Subject	System	Topic

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A 63-year-old man comes to the emergency department due to muscle weakness with severe cramping in the lower extremities. The cramps are severe enough to disrupt his sleep. The patient also exercises daily but has had to suspend his exercise regimen in the last 3 days due to the symptoms. Past medical history is notable for hypertension, for which he was started on chlorthalidone and amlodipine 4 weeks ago. Blood pressure in the emergency department is 140/86 mm Hg and pulse is 90/min. The heart has a regular rate and rhythm, and he has palpable pedal pulses with no peripheral edema. Which of the following is the most likely cause of this patient's muscular symptoms?

A. Hyperuricemia
B. Hypocalcemia
C. Hypoglycemia
D. Hypokalemia
E. Hyponatremia
F. Hypophosphatemia

Submit

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- A. Hyperuricemia (5%)
- B. Hypocalcemia (25%)
- C. Hypoglycemia (1%)
- ✓ D. Hypokalemia (58%)
- E. Hyponatremia (6%)
- F. Hypophosphatemia (2%)

Omitted
Correct answer
D

58%
Answered correctly

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Time Spent

05/03/2020
Last Updated

Explanation

Thiazide diuretics lower blood pressure by decreasing **intravascular volume**, reducing cardiac output, and lowering systemic vascular resistance. Thiazides inhibit Na^+/Cl^- co-transporters in the distal convoluted tubules, thereby decreasing reabsorption of Na^+ and Cl^-. The decrease in intravascular volume is partially attenuated by activation of the **renin-angiotensin-aldosterone** system. However, the rise in aldosterone secretion leads to increased urinary excretion of potassium and hydrogen ions, with resulting **hypokalemia** and metabolic alkalosis.

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Chlorthalidone appears to be more potent in lowering blood pressure than other thiazides (eg, hydrochlorothiazide) but is also associated with more metabolic abnormalities. Significant hypokalemia can cause **muscle weakness**, cramps, and possible rhabdomyolysis.

(Choice A) Hypovolemia stimulates uric acid reabsorption in the proximal tubules. This can cause hyperuricemia and potentially precipitate a gout attack (acute monoarticular arthritis).

(Choice B) Thiazides increase calcium reabsorption in the distal convoluted tubules, reducing urinary excretion of calcium and modestly raising serum calcium levels. They do not cause hypocalcemia.

(Choice C) Thiazides decrease insulin secretion and peripheral uptake of glucose. This can cause hyperglycemia, not hypoglycemia.

(Choice E) Thiazides can cause hyponatremia due to increased urinary excretion of sodium. Acute hyponatremia causes nausea, malaise, headache, and central nervous symptoms (eg, altered mental status, seizures). Muscle cramps are less common and usually seen with chronic hyponatremia.

(Choice F) Hypophosphatemia can cause muscle weakness and paralysis but is not a side effect of thiazides. It is commonly seen in alcoholics.

Educational objective:
Thiazide diuretics decrease intravascular fluid volume, which stimulates aldosterone secretion and leads to increased excretion of potassium and hydrogen ions in the urine. This results in hypokalemia and metabolic alkalosis.

References

- Thiazides and the risk of hypokalemia in the general population.

Pharmacology	Renal, Urinary Systems & Electrolytes	Hypokalemia
Subject	System	Topic

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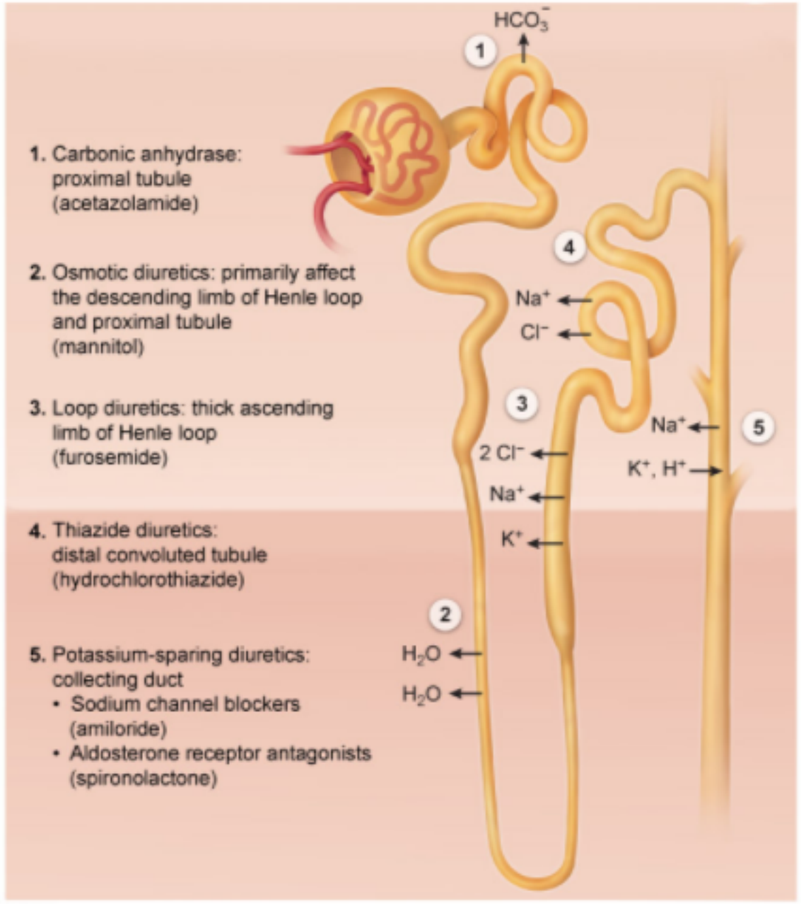
Exhibit Display

Site of inhibition for various diuretics



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Subject System Topic

resistance. Thiazides inhibit Na^+/Cl^- co-transporters in the distal convoluted tubules, thereby decreasing reabsorption of Na^+ and Cl^-. The decrease in intravascular volume is partially attenuated by activation of the **renin-angiotensin-aldosterone** system. However, the rise in aldosterone secretion leads to increased urinary excretion of potassium and hydrogen ions, with resulting **hypokalemia** and metabolic alkalosis.

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Pharmacology	Renal, Urinary Systems & Electrolytes	Hypokalemia
Subject	System	Topic

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A 36-year-old woman with end-stage renal disease secondary to type 1 diabetes mellitus comes to the office for routine examination. The patient's medical history includes hypertension, diabetic retinopathy, and neuropathy. Hemodialysis was started 2 months ago along with an erythropoiesis-stimulating agent. She takes daily long- and short-acting insulin, lisinopril, and calcitriol. Her hemoglobin has increased from 7.4 g/dL to 10.2 g/dL over the past 2 months. Which of the following complications is most likely to be seen with the agent used to treat this patient's anemia?

A. Angioedema
B. Diarrhea
C. Hyperkalemia
D. Hypoglycemia
E. Mineral bone disease
F. Worsening hypertension

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- A. Angioedema (10%)
- B. Diarrhea (4%)
- C. Hyperkalemia (11%)
- D. Hypoglycemia (6%)
- E. Mineral bone disease (16%)
- ✓ F. Worsening hypertension (50%)

Omitted
Correct answer
F

50%
Answered correctly

02 secs
Time Spent

03/29/2020
Last Updated

Explanation

Erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin alpha) can be used to treat **anemia of chronic kidney disease** (CKD), which usually develops at a glomerular filtration rate of <30 mL/min. Untreated anemia in CKD and dialysis patients can lead to cardiac dysfunction, fatigue, weakness, and possible mental status changes (eg, decreased cognition). ESAs can substantially improve anemia, avoiding the need for blood transfusions. However, ESAs are associated with increased risk for **thromboembolic events** (eg, vascular graft thrombosis,

Explanation

Erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin, darbepoetin alpha) can be used to treat **anemia of chronic kidney disease** (CKD), which usually develops at a glomerular filtration rate of <30 mL/min. Untreated anemia in CKD and dialysis patients can lead to cardiac dysfunction, fatigue, weakness, and possible mental status changes (eg, decreased cognition). ESAs can substantially improve anemia, avoiding the need for blood transfusions. However, ESAs are associated with increased risk for **thromboembolic events** (eg, vascular graft thrombosis, stroke) due to increased blood viscosity, as a result of the elevation in red cell mass. Many patients also develop **hypertension**, possibly due to activation of erythropoietin receptors on vascular endothelial and smooth muscle cells.

(Choice A) Angioedema is a possible side effect of lisinopril, an ACE inhibitor. ACE inhibition causes impaired inactivation of bradykinin (a vasoactive peptide), leading to vasodilation, hypotension, and possible angioedema.

(Choices B and D) Iron supplements can cause constipation, diarrhea, nausea, and epigastric pain. Long-acting insulin is usually cleared by the kidneys and can predispose CKD patients to hypoglycemia. However, ESAs are usually not associated with diarrhea or hypoglycemia.

(Choice C) Hyperkalemia is a frequent complication of acute kidney disease and CKD. However, it is not a common side effect of ESAs.

(Choice E) Mineral bone disease can be a complication of CKD due to secondary hyperparathyroidism, leading to calcium loss from bone. However, it is not a side effect of this patient's medications.

Educational objective:
Erythropoiesis-stimulating agents (ESAs) can substantially improve anemia symptoms, avoiding the need for blood transfusions in chronic kidney disease and dialysis patients. However, ESAs are associated with increased risk for hypertension and thromboembolic events.

References

- The cardiovascular effects of erythropoietin.

Pharmacology	Renal, Urinary Systems & Electrolytes	Erythropoietin
Subject	System	Topic

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A 30-year-old Caucasian male presents to your office with fatigue, muscle weakness and occasional headaches. His blood pressure is 180/110 mmHg and his heart rate is 80/min. Laboratory evaluation reveals low serum potassium, severely depressed plasma renin activity, and a CT scan demonstrates a right-sided adrenal mass. After treatment for several weeks, the patient's symptoms resolve, his blood pressure is decreased to 130/70 mmHg and his heart rate is 75/min. Which of the following drugs was most likely used in this patient?

- A. Clonidine
- B. Propranolol
- C. Captopril
- D. Hydrochlorothiazide
- E. Eplerenone
- F. Verapamil
- G. Amlodipine
- H. Isosorbide dinitrate

Submit

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- A. Clonidine (8%)
- B. Propranolol (9%)
- C. Captopril (12%)
- D. Hydrochlorothiazide (6%)
- ✓ E. Eplerenone (55%)
- F. Verapamil (1%)
- G. Amlodipine (3%)
- H. Isosorbide dinitrate (1%)

Omitted
Correct answer
E

55%
Answered correctly

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06/11/2020
Last Updated

Explanation

This patient is suffering from an aldosterone secreting tumor (adenoma) leading to primary hyperaldosteronism (Conn's Syndrome). Presenting

Explanation

This patient is suffering from an aldosterone secreting tumor (adenoma) leading to primary hyperaldosteronism (Conn's Syndrome). Presenting signs of hyperaldosteronism most commonly include hypertension, hypokalemia, metabolic alkalosis and decreased plasma renin activity. Aldosterone causes resorption of sodium and water and wasting of potassium and hydrogen ions (acid) at the distal portion of the nephron, leading to hypokalemia and alkalosis. Additionally, inappropriately high aldosterone will suppress renin activity as part of a feedback inhibition loop. The treatment for a unilateral adenoma secreting aldosterone, as is found in this patient, can be either by surgical resection or by medical therapy with aldosterone antagonists. Spironolactone is the most frequently used first-line drug, and eplerenone is a new aldosterone antagonist that has fewer side effects than spironolactone and is often used in those that can not tolerate spironolactone.

The most frequently mentioned side effect of these medications is their ability to cause gynecomastia (approximately 1% with eplerenone, 9% with spironolactone).

Other drugs mentioned in the other choices are not commonly used in Conn's syndrome.

Educational objective:
Aldosterone excess will cause hypertension, hypokalemia, metabolic alkalosis and depressed renin. Alternatively, hypoaldosteronism is the cause of type IV renal tubular acidosis. Aldosterone antagonists such as spironolactone or eplerenone can be used as medical therapy for Conn's syndrome.

References

- Treatment of primary aldosteronism.
- The pharmacological treatment of primary aldosteronism.

Pharmacology	Renal, Urinary Systems & Electrolytes	Hyperaldosteronism
Subject	System	Topic

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A 75-year-old man comes to the office for follow-up of hypertension. In recent weeks, his blood pressure has consistently been 160-165/85-90 mm Hg. Medical history includes a right carotid endarterectomy for recurrent transient ischemic attacks, a myocardial infarction 2 years ago, and coronary artery bypass surgery for unstable angina 1 year ago. The patient currently takes metoprolol, clopidogrel, amlodipine, and rosuvastatin. He quit smoking 20 years ago and does not drink alcohol. The patient is compliant with his medical therapy and office visits. Ramipril is added to his medication regimen. One week later, creatinine is 2.1 mg/dL, up from a baseline of 1.1 mg/dL. Assuming the patient's baseline urinalysis is normal, a repeat urinalysis at this time would most likely reveal which of the following?

	Protein	Red blood cells	White blood cells	Casts	Other findings
A.	2+	50	10	RBC	none
B.	1+	0-1	50	WBC	eosinophils
C.	-	50	0-1	none	needle-shaped crystals
D.	4+	0-1	0-1	none	oval fat bodies
E.	-	0-1	0-1	none	none

Submit

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A. (11%)	2+	50	10	RBC	none
B. (9%)	1+	0-1	50	WBC	eosinophils
C. (2%)	-	50	0-1	none	needle-shaped crystals
D. (8%)	4+	0-1	0-1	none	oval fat bodies
✓ E. (68%)	-	0-1	0-1	none	none

Omitted
Correct answer
E

68%
Answered correctly

02 secs
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03/10/2020
Last Updated

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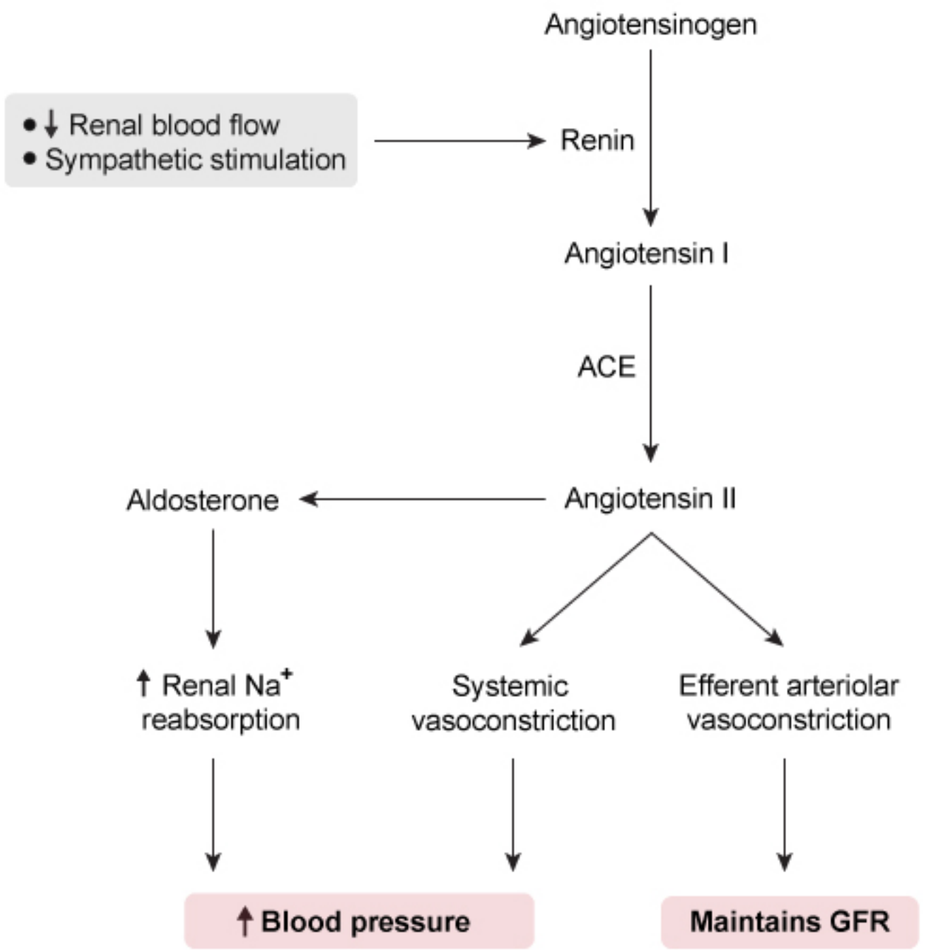
Renin-angiotensin-aldosterone system & antihypertensives



GFR = glomerular filtration rate.

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This patient has **widespread atherosclerosis** (cerebrovascular and coronary) and significant atherosclerotic risk factors (ie, hypertension, smoking). His persistent hypertension despite multiple medications suggests **renal artery stenosis** (RAS) due to atherosclerotic disease involving the renal arteries. Narrowing of the renal artery causes a reduction in renal blood flow and a decreased glomerular filtration rate (GFR) due to reduced hydrostatic pressure. This stimulates renin production, which leads to **angiotensin II** formation. Angiotensin II causes systemic vasoconstriction with a resultant rise in blood pressure, thereby increasing renal perfusion.

In the kidney, angiotensin II preferentially **constricts the efferent arteriole**, which increases glomerular filtration. Blockade of this response by **ACE inhibitors** (eg, ramipril) or angiotensin II receptor blockers (eg, losartan) causes the filtration pressure to fall, leading to a **reduced GFR**. In unilateral RAS, the normal kidney compensates for the decreased GFR, and overall creatinine clearance is maintained. However, patients with bilateral RAS often develop a rise in serum creatinine with initiation of ACE inhibitors. Because the glomeruli and renal tubules are otherwise normal, **urinalysis** is typically **unremarkable** (ie, no hematuria, proteinuria, or casts).

(Choice A) Acute renal failure and hypertension with red blood cell casts, hematuria, sterile pyuria, and proteinuria suggest glomerulonephritis. However, glomerulonephritis is often associated with systemic conditions (eg, lupus, recent infections), not ACE inhibitor use.

(Choice B) White blood cell casts, sterile pyuria, and urine eosinophils suggest acute interstitial nephritis, which often occurs after new medication introduction. However, it is often accompanied by rash, fever, and eosinophilia.

(Choice C) Crystal precipitation in the urine can cause kidney injury and hematuria but typically presents with flank pain. In addition, acyclovir (not ramipril) causes needle-shaped crystal precipitation in the urine.

(Choice D) Oval fat bodies and significant proteinuria are seen in nephrotic syndromes (eg, membranous nephropathy, minimal change disease), which can cause acute kidney injury and hyperlipidemia. However, patients typically have significant edema, and nephrotic syndromes are not associated with ACE inhibitor use.

Educational objective:
In renal artery stenosis, increased production of angiotensin II causes increased systemic blood pressure (to increase renal perfusion) and preferential constriction of the glomerular efferent arteriole (to increase glomerular filtration). Patients with bilateral renal artery stenosis are dependent on this response to maintain renal function; initiation of ACE inhibitors or angiotensin II receptor blockers can precipitate acute renal failure. However, urinalysis is typically unremarkable (ie, no hematuria, proteinuria, or casts).

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Educational objective:
In renal artery stenosis, increased production of angiotensin II causes increased systemic blood pressure (to increase renal perfusion) and preferential constriction of the glomerular efferent arteriole (to increase glomerular filtration). Patients with bilateral renal artery stenosis are dependent on this response to maintain renal function; initiation of ACE inhibitors or angiotensin II receptor blockers can precipitate acute renal failure. However, urinalysis is typically unremarkable (ie, no hematuria, proteinuria, or casts).

References

- Epidemiology and optimal management in patients with renal artery stenosis.

Pharmacology	Renal, Urinary Systems & Electrolytes	Renal artery stenosis
Subject	System	Topic

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A 52-year-old woman comes to the office due to episodic incontinence for the last several months. She states that these episodes occur almost every day and are very embarrassing. They begin as an urge to urinate, and most of the time she cannot make it to the bathroom before urinating on herself. Physical examination, including pelvic examination, is unremarkable. A urinalysis is within normal limits. Urodynamic evaluation is significant for detrusor instability. Initial non-pharmacologic measures are unsuccessful and pharmacologic therapy is considered. The appropriate treatment for this patient's condition includes an agent with which of the following effects?

A. Antagonism of alpha-1 adrenoreceptors

B. Antagonism of beta-1 adrenoreceptors

C. Antagonism of muscarinic cholinergic receptors

D. Antagonism of nicotinic cholinergic receptors

E. Stimulation of alpha-2 adrenoreceptors

F. Stimulation of beta-2 adrenoreceptors

Submit

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- A. Antagonism of alpha-1 adrenoreceptors (8%)
- B. Antagonism of beta-1 adrenoreceptors (1%)
- ✓ C. Antagonism of muscarinic cholinergic receptors (79%)
- D. Antagonism of nicotinic cholinergic receptors (3%)
- E. Stimulation of alpha-2 adrenoreceptors (3%)
- F. Stimulation of beta-2 adrenoreceptors (2%)

Omitted
Correct answer
C

79%
Answered correctly

02 secs
Time Spent

04/05/2020
Last Updated

Explanation

This patient has **urge incontinence**, or overactive bladder syndrome, which is caused by uninhibited bladder contractions (detrusor instability). This causes a sudden sensation of urgency, with involuntary leakage of urine often occurring before reaching the toilet.

Pharmacologic therapy with **anticholinergic drugs** is useful for treating the condition. These agents (eg, oxybutynin) antagonize muscarinic

Receptor	Target organ(s)	Effect of stimulation	Effect of inhibition
M_1	Brain	Memory formation/cognitive functioning	Confusion
M_2	Heart	Decreased heart rate & atrial contraction	Increased heart rate & contractility
M_3	Peripheral vasculature	Smooth muscle relaxation, vasodilation, hypotension	Smooth muscle contraction, vasoconstriction, hypertension
	Lung	Bronchoconstriction	Bronchodilation
	Bladder	Detrusor contraction	Detrusor relaxation, urinary retention
	Eyes	Pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)	Mydriasis, cycloplegia, may precipitate acute angle glaucoma in elderly patients
	Gastrointestinal	Increased peristalsis, increased salivary & gastric secretions	Constipation, dry mouth, decreased acid production

M_3	Eyes	Pupillary sphincter muscle contraction (miosis), ciliary muscle contraction (accommodation)	Mydriasis, cycloplegia, may precipitate acute angle glaucoma in elderly patients
	Gastrointestinal	Increased peristalsis, increased salivary & gastric secretions	Constipation, dry mouth, decreased acid production
	Skin	Increased sweat production	Increased temperature (from decreased sweating)

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This patient has **urge incontinence**, or overactive bladder syndrome, which is caused by uninhibited bladder contractions (detrusor instability). This causes a sudden sensation of urgency, with involuntary leakage of urine often occurring before reaching the toilet.

Pharmacologic therapy with **anticholinergic drugs** is useful for treating the condition. These agents (eg, oxybutynin) antagonize muscarinic receptors, primarily the **M_3 receptors** present on smooth muscle cells in the bladder. Antagonism of M_3 receptors decreases the production of IP_3 and the release of calcium, leading to smooth muscle relaxation. This causes **decreased involuntary detrusor contractions**, increased bladder capacity, and decreased sense of urgency.

Antimuscarinic agents often act on several types of muscarinic receptors and should be used with caution, especially in elderly patients. These agents should be started at the lowest possible dose and titrated as needed to minimize anticholinergic side effects (dry mouth, blurred vision, tachycardia, drowsiness, and constipation).

(Choice A) Alpha1-blockers such as doxazosin, prazosin and terazosin are useful for the treatment of both benign prostatic hyperplasia (BPH) and hypertension. They cause relaxation of the smooth muscle in arterial and venous walls, leading to a decrease in peripheral vascular resistance. In patients with BPH, they also induce relaxation of the smooth muscle in the bladder neck and prostate, leading to a decrease in

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(Choice B) Beta-1 receptors are found in cardiac tissue and on renal juxtaglomerular cells. Selective beta-1 blockers (eg, metoprolol) decrease heart rate and contractility, and block catecholamine-induced renin release by the kidney.

(Choice D) Nicotinic cholinergic receptors are found on postganglionic neurons in sympathetic and parasympathetic ganglia and on skeletal muscle cells at the neuromuscular junction. Drugs that block skeletal muscle nicotinic receptors, such as tubocurarine, are often used during general anesthesia to induce paralysis.

(Choice E) Central sympatholytics such as methyldopa and clonidine stimulate alpha-2 receptors centrally, which causes a decrease in generalized sympathetic outflow and a decrease in blood pressure. Rebound hypertension is a concern with abrupt cessation.

(Choice F) Beta-2 adrenergic receptors are located in the smooth muscle of airways, peripheral vasculature, and uterus. Stimulation of these receptors causes bronchodilation, vasodilation, and tocolysis, respectively. In contrast, bladder relaxation is mediated primarily by beta-3 adrenergic receptors.

Educational objective:

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Educational objective:
Urge incontinence, or overactive bladder syndrome, is caused by uninhibited bladder contractions (detrusor instability). It results in a sense of urgency accompanied by an involuntary loss of urine. If behavioral therapy alone is unsuccessful, pharmacologic therapy with an antimuscarinic drug (targeting M_3 receptors) can help improve symptoms.

References

- Antimuscarinic agents: implications and concerns in the management of overactive bladder in the elderly.

Pharmacology	Renal, Urinary Systems & Electrolytes	Urinary incontinence
Subject	System	Topic

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A 44-year-old woman comes to the office for a follow-up appointment. Six months earlier, the patient was diagnosed with essential hypertension; she has followed dietary and exercise recommendations since then. At a follow-up visit 3 months ago, she reported episodic headaches due to migraines. Her blood pressure at that visit was 145/92 mm Hg. Antihypertensive therapy with a beta blocker was started due to its beneficial effect on migraine prophylaxis. Now, 3 months later, the patient's blood pressure has decreased to 120/80 mm Hg. She is compliant with her medication and has had no serious adverse effects. Which of the following is the most likely combination of changes in response to this patient's treatment (AT = Angiotensin)?

	Renin	AT I	AT II	Aldosterone	Bradykinin
A.	↓	↓	↓	↓	No change
B.	↑	↓	↓	↓	No change
C.	↑	↑	↓	↓	↓
D.	↑	↑	↓	↓	↑
E.	↑	↑	↑	↓	No change
F.	↑	↑	↑	↑	No change

Submit

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	Renin	AT I	AT II	Aldosterone	Bradykinin
✓ A. (73%)	↓	↓	↓	↓	No change
B. (3%)	↑	↓	↓	↓	No change
C. (2%)	↑	↑	↓	↓	↓
D. (5%)	↑	↑	↓	↓	↑
E. (3%)	↑	↑	↑	↓	No change
F. (11%)	↑	↑	↑	↑	No change

Omitted
Correct answer
A

73%
Answered correctly

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Time Spent

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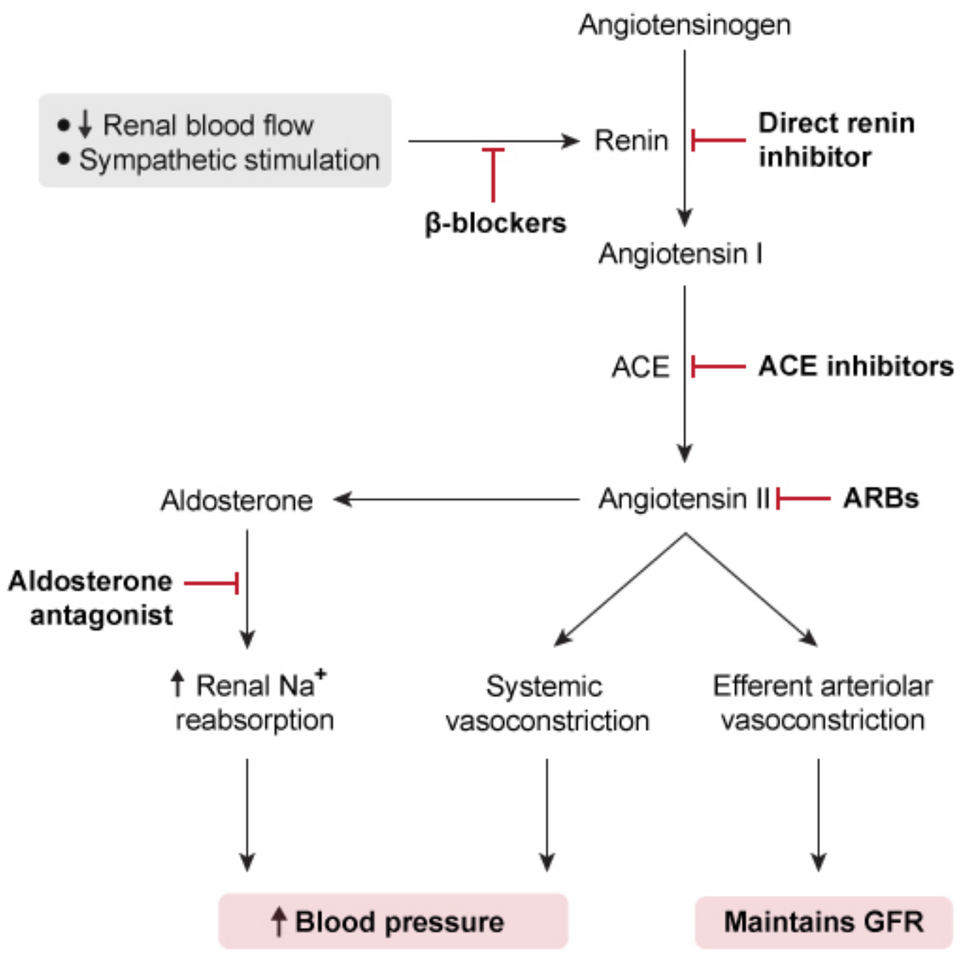
Renin-angiotensin-aldosterone system & antihypertensives



GFR = glomerular filtration rate.

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The renin-angiotensin-aldosterone system (RAAS) is the most important neurohormonal system regulating sodium/fluid balance and arterial blood pressure in the body. Regulation of the RAAS involves 3 major components: macula densa (distal tubule sodium sensor), intrarenal baroreceptors, and beta-adrenergic receptors. Beta-adrenergic regulation is mediated through sympathetic stimulation of **beta-1 receptors** located on juxtaglomerular cells, which stimulate the release of renin.

Beta-adrenergic antagonists inhibit renin release, which in turn reduces the conversion of angiotensinogen to angiotensin I and reduces the levels of angiotensin II and aldosterone. This effect on the RAAS is only partially responsible for beta blocker effects on blood pressure, and antihypertensive efficacy of beta blockers weakly correlates with plasma renin levels. Beta blockers have no effect on ACE activity and, therefore, do not affect bradykinin levels.

(Choice B) Direct renin inhibitors (aliskiren) block the conversion of angiotensinogen to angiotensin I, which leads to reduced levels of angiotensin I and II and aldosterone. Plasma renin concentration is increased via suppression of the inhibitory feedback loop.

(Choices C and D) ACE inhibitors prevent the conversion of angiotensin I to angiotensin II and lead to decreased levels of angiotensin II and aldosterone, along with increased plasma renin activity and angiotensin I levels via inhibition of negative feedback. ACE is also a kininase and normally degrades bradykinin in the body. Therefore, ACE inhibitors lead to increased levels of bradykinin, which is responsible for the coughing seen in treated patients.

(Choice E) Angiotensin II receptor blockers (ARBs) block the action of angiotensin II on angiotensin (AT1) receptors, which leads to increased levels of renin and angiotensin I and II. ARBs have no effect on bradykinin levels.

(Choice F) Aldosterone antagonists (spironolactone, eplerenone) compete with aldosterone for the receptor sites in the distal tubules. They raise the levels of renin, angiotensin I and II, and aldosterone via inhibition of negative feedback.

Educational objective:
Beta-adrenergic blocking drugs inhibit renin release by blocking beta-1 receptor-mediated regulation of the renin-angiotensin-aldosterone system. This reduces plasma renin activity, with a resulting reduction in angiotensin I, angiotensin II, and aldosterone levels.

References

- Beta-adrenergic receptor blockade as a therapeutic approach for suppressing the renin-angiotensin-aldosterone system in normotensive and hypertensive subjects.

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A 46-year-old man comes to the emergency department with flank pain and hematuria. The pain is similar to several previous episodes of kidney stones. Abdominal imaging reveals a radiopaque calculus in the right ureter. The patient is admitted to the hospital and given intravenous hydration and analgesics. He subsequently passes the stone with rapid relief of his symptoms. Chemical analysis reveals that the stone is composed primarily of calcium oxalate. Which of the following medications is most likely to prevent recurrent stone formation in this patient?

A. Acetazolamide

B. Furosemide

C. Hydrochlorothiazide

D. Mannitol

E. Triamterene

Submit

A 46-year-old man comes to the emergency department with flank pain and hematuria. The pain is similar to several previous episodes of kidney stones. Abdominal imaging reveals a radiopaque calculus in the right ureter. The patient is admitted to the hospital and given intravenous hydration and analgesics. He subsequently passes the stone with rapid relief of his symptoms. Chemical analysis reveals that the stone is composed primarily of calcium oxalate. Which of the following medications is most likely to prevent recurrent stone formation in this patient?

- A. Acetazolamide (10%)
- B. Furosemide (10%)
- ✓ C. Hydrochlorothiazide (73%)
- D. Mannitol (1%)
- E. Triamterene (2%)

Omitted
Correct answer
C

73%
Answered correctly

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Explanation

Effect of thiazide diuretics on distal tubular calcium reabsorption

Interstitial	Distal tubule cells	Tubular

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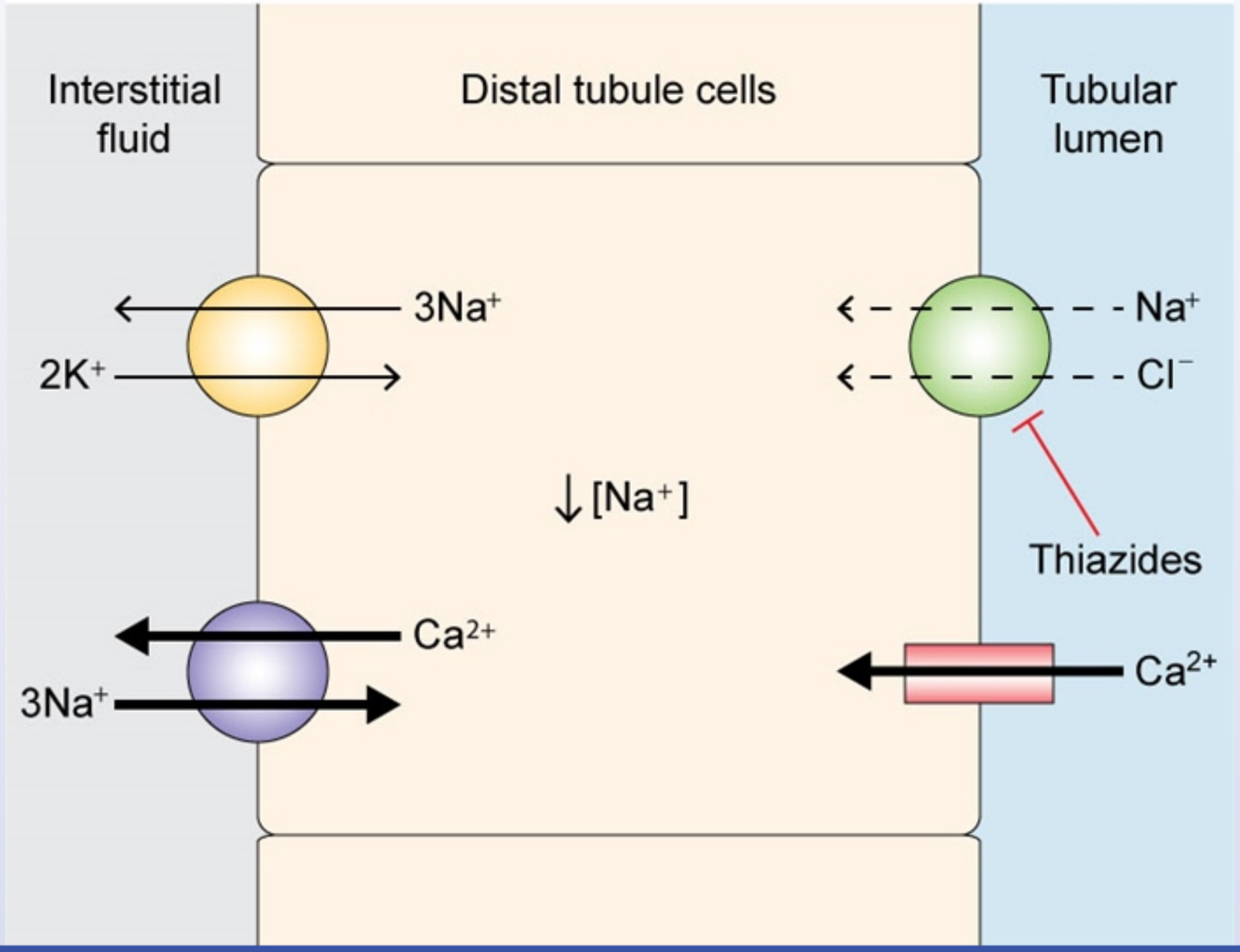
Effect of thiazide diuretics on distal tubular calcium reabsorption



Hypercalciuria increases the formation of calcium (calcium oxalate and calcium phosphate) stones, the most common types of kidney stone. In patients with recurrent calcium nephrolithiasis, **thiazide diuretics** can help prevent stone formation by decreasing urine Ca^{2+} excretion.

Thiazides increase Ca^{2+} reabsorption through 2 major mechanisms:

1. **Inhibition of the Na^+/Cl^- cotransporter** on the apical side of distal convoluted tubule cells decreases intracellular Na^+ concentrations. This activates the basolateral Na^+/Ca^{2+} antiporter, which pumps Na^+ into the cell in exchange for Ca^{2+}. The resulting decrease in intracellular Ca^{2+} concentration enhances luminal Ca^{2+} reabsorption across the apical membrane.
2. **Hypovolemia** induced by thiazides increases Na^+ and H_2O reabsorption in the proximal tubule, leading to a passive increase in paracellular Ca^{2+} reabsorption.

(Choice A) Acetazolamide is a carbonic anhydrase inhibitor that acts on the proximal convoluted tubule to cause bicarbonate wasting, raising urine pH and decreasing the risk of uric acid stones. However, the resulting systemic acidosis may increase release of calcium phosphate from bone, which is then cleared by the kidneys. Some studies have found that acetazolamide use may raise the risk of calcium stone formation.

(Choice B) Ca^{2+} reabsorption in the loop of Henle occurs through both the transcellular and paracellular pathways. Paracellular Ca^{2+} reabsorption depends on concurrent, transcellular $Na^+/K^+/Cl^-$ reabsorption. Loop diuretics (eg, furosemide) block the Na-K-2Cl cotransporter and increase urinary Ca^{2+} excretion.

(Choice D) Mannitol is an osmotic diuretic. It is not used as maintenance therapy for any indication as it causes volume depletion and hypernatremia with prolonged use. It has no effect on Ca^{2+} homeostasis.

(Choice E) Triamterene and amiloride are potassium-sparing diuretics that inhibit Na^+ reabsorption in the collecting duct by blocking the epithelial sodium channel. This decreases net Na^+/K^+ exchange, reducing serum K^+ losses.

Educational objective:
Thiazide diuretics effectively increase renal calcium reabsorption. In patients with recurrent calcium nephrolithiasis, thiazide diuretics can help prevent stone formation by decreasing urine Ca^{2+} excretion.

References

- The mechanism of hypocalciuria with NaCl cotransporter inhibition.

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A 30-year-old woman is evaluated for almost daily headaches and intermittent blurry vision. Medical history includes obesity but no other chronic conditions. Physical examination shows bilateral symmetric papilledema. There are no other focal neurological deficits. Brain imaging is normal, and blood cell counts and serum chemistry studies are within normal limits. Lumbar puncture reveals elevated opening pressure, and idiopathic intracranial hypertension is diagnosed. Weight loss is advised, and the patient is prescribed acetazolamide therapy. Which of the following changes are most likely to occur in this patient over the next several days due to the medication?

	$PaCO_2$	Serum calcium	Urine potassium	Urine pH
A.	Decrease	Decrease	Increase	Increase
B.	Decrease	No change	Increase	Increase
C.	Decrease	No change	Decrease	Increase
D.	Increase	Decrease	Increase	Decrease
E.	Increase	Increase	Increase	Decrease

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	$PaCO_2$	Serum calcium	Urine potassium	Urine pH
A. (12%)	Decrease	Decrease	Increase	Increase
✓ B. (57%)	Decrease	No change	Increase	Increase
C. (16%)	Decrease	No change	Decrease	Increase
D. (8%)	Increase	Decrease	Increase	Decrease
E. (4%)	Increase	Increase	Increase	Decrease

Omitted
Correct answer
B

57%
Answered correctly

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Time Spent

04/22/2020
Last Updated

Explanation

Explanation

Diuretic effects on total body electrolyte levels					
Diuretic type	**Na^+**	**K^+**	**HCO_3^-**	**Ca^{2+}**	**Uric acid**
Loop (eg, furosemide)	↓↓↓	↓↓	↑↑	↓	↑
Thiazide (eg, HCTZ, metolazone)	↓↓	↓	↑	↑	↑
Potassium sparing (eg, spironolactone, amiloride)	↓	↑	↓	—	—
Carbonic anhydrase inhibitor (eg, acetazolamide)	↓	↓	↓	—	—
HCTZ = hydrochlorothiazide.					

Acetazolamide is a **carbonic anhydrase inhibitor** that acts as a weak diuretic. The drug also reduces intracranial pressure and improves symptoms in patients with **idiopathic intracranial hypertension**. This effect occurs independent of the kidneys and likely results from a decreased rate of cerebrospinal fluid production by the choroid plexus.

Carbonic anhydrase inhibitors **block reabsorption of sodium bicarbonate** ($NaHCO_3$) in the proximal tubule, leading to **increased excretion of HCO_3^-**. This **alkalinizes the urine** (increased pH) while reducing blood pH to create **mild metabolic acidosis**. The overall diuretic effect is weak because most of the Na^+ blocked from reabsorption in the proximal tubule is reabsorbed more distally. The distal reabsorption of Na^+ stimulates increased K^+ excretion (and relatively insignificant increased H^+ excretion), leading to **increased urine potassium** and mild hypokalemia. There is no significant effect on Ca^{2+} or other electrolytes **(Choice A)**.

In response to the mild metabolic acidosis, ventilation is increased to facilitate CO_2 removal and **decrease blood $PaCO_2$** (compensatory respiratory alkalosis).

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In response to the mild metabolic acidosis, ventilation is increased to facilitate CO_2 removal and **decrease blood $PaCO_2$** (compensatory respiratory alkalosis).

(Choice C) Potassium-sparing diuretics (eg, spironolactone) block Na^+ reabsorption in the collecting duct while increasing the reabsorption of K^+ and H^+. This decreases urine potassium and increases urine pH. Mild metabolic acidosis is generated with compensatory respiratory alkalosis. Ca^{2+} and other electrolytes are not significantly affected.

(Choice D) Loop diuretics (eg, furosemide) block the $Na^+K^+2Cl^-$ transporter in the ascending loop of Henle. This causes potent excretion of Na^+, K^+, and Cl^- (increased urine potassium) and impairs passive Ca^{2+} reabsorption, decreasing serum calcium. There is also aldosterone-mediated H^+ loss, and the Cl^- depletion impairs HCO_3^- excretion, leading to decreased urine pH and metabolic alkalosis with compensatory respiratory acidosis (increased $PaCO_2$).

(Choice E) Thiazide diuretics (eg, hydrochlorothiazide) block the Na^+Cl^- transporter in the distal convoluted tubule. Ca^{2+} reabsorption is increased, leading to increased serum calcium. Otherwise, the effects are the same as those with loop diuretics but with less potency.

Educational objective:
Carbonic anhydrase inhibitors (eg, acetazolamide) are weak diuretics that block reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule. The main effect is increased HCO_3^- excretion, leading to increased urine pH, mild metabolic acidosis (with compensatory respiratory alkalosis), and mild hypokalemia.

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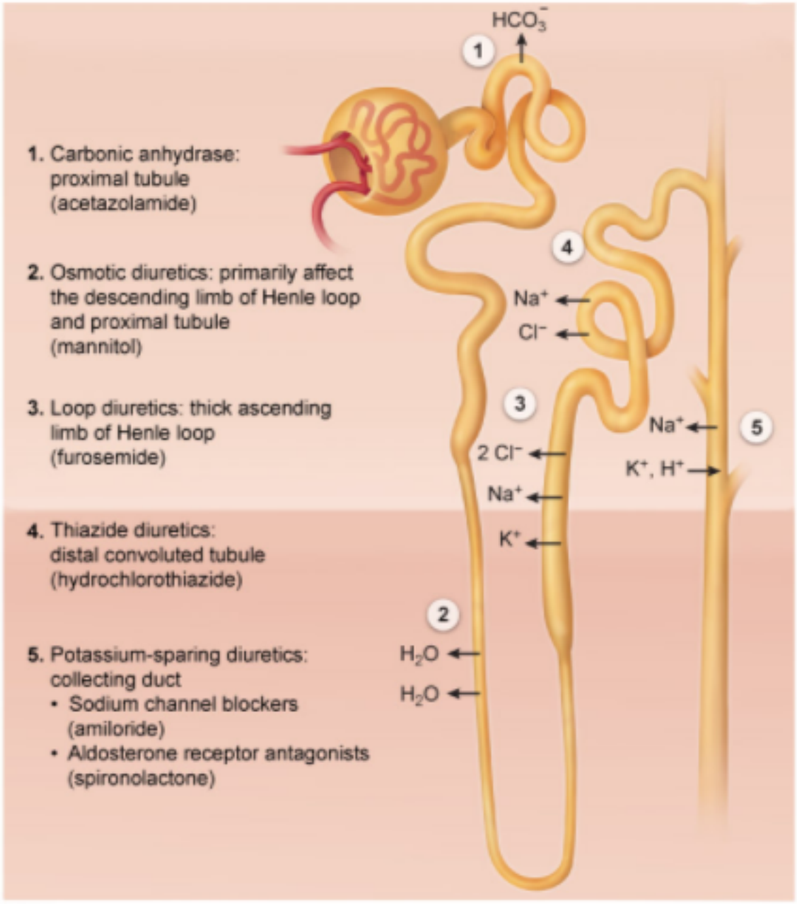
Exhibit Display

Site of inhibition for various diuretics



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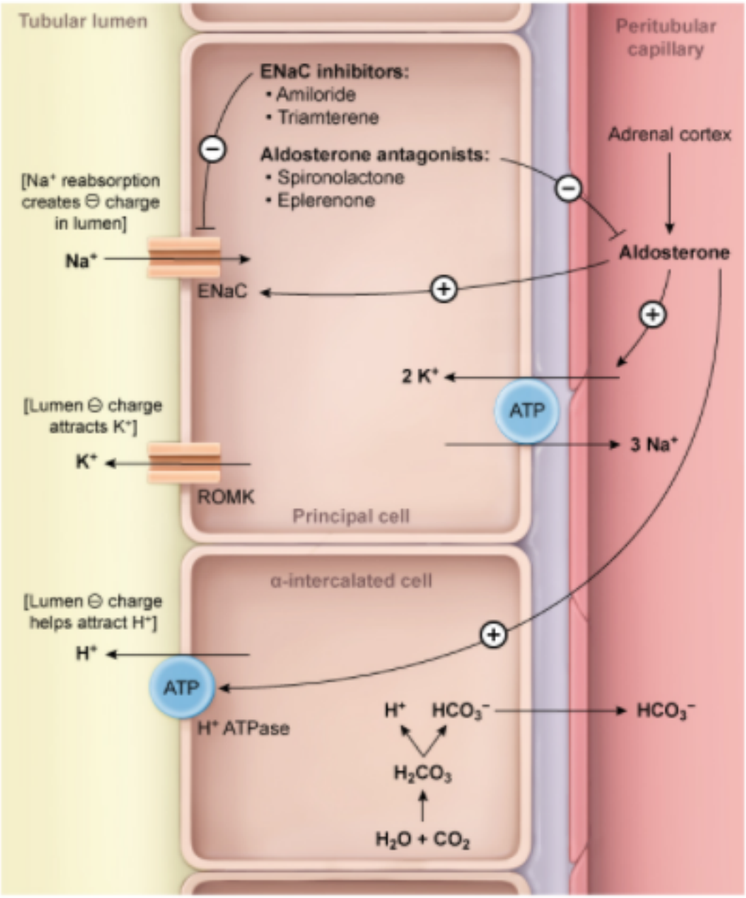
symptoms in patients with **idiopathic intracranial hypertension**. This effect occurs independent of the kidneys and likely results from a

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



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Subject System Topic

Carbonic anhydrase inhibitors **block reabsorption of sodium bicarbonate** ($NaHCO_3$) in the proximal tubule, leading to **increased excretion of HCO_3^-**. This **alkalinizes the urine** (increased pH) while reducing blood pH to create **mild metabolic acidosis**. The overall diuretic effect is weak because most of the Na^+ blocked from reabsorption in the proximal tubule is reabsorbed more distally. The distal reabsorption of Na^+ stimulates increased K^+ excretion (and relatively insignificant increased H^+ excretion), leading to **increased urine potassium** and mild hypokalemia. There is no significant effect on Ca^{2+} or other electrolytes **(Choice A)**.

In response to the mild metabolic acidosis, ventilation is increased to facilitate CO_2 removal and **decrease blood $PaCO_2$** (compensatory respiratory alkalosis).

(Choice C) Potassium-sparing diuretics (eg, spironolactone) block Na^+ reabsorption in the collecting duct while increasing the reabsorption of K^+ and H^+. This decreases urine potassium and increases urine pH. Mild metabolic acidosis is generated with compensatory respiratory alkalosis. Ca^{2+} and other electrolytes are not significantly affected.

(Choice D) Loop diuretics (eg, furosemide) block the $Na^+K^+2Cl^-$ transporter in the ascending loop of Henle. This causes potent excretion of Na^+, K^+, and Cl^- (increased urine potassium) and impairs passive Ca^{2+} reabsorption, decreasing serum calcium. There is also aldosterone-mediated H^+ loss, and the Cl^- depletion impairs HCO_3^- excretion, leading to decreased urine pH and metabolic alkalosis with compensatory respiratory acidosis (increased $PaCO_2$).

(Choice E) Thiazide diuretics (eg, hydrochlorothiazide) block the Na^+Cl^- transporter in the distal convoluted tubule. Ca^{2+} reabsorption is increased, leading to increased serum calcium. Otherwise, the effects are the same as those with loop diuretics but with less potency.

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Carbonic anhydrase inhibitors (eg, acetazolamide) are weak diuretics that block reabsorption of sodium bicarbonate ($NaHCO_3$) in the proximal tubule. The main effect is increased HCO_3^- excretion, leading to increased urine pH, mild metabolic acidosis (with compensatory respiratory alkalosis), and mild hypokalemia.

Pharmacology	Renal, Urinary Systems & Electrolytes	Metabolic acidosis
Subject	System	Topic

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A 65-year-old man comes to the office for follow-up monitoring of type 2 diabetes mellitus. He was diagnosed with diabetes 7 years ago and follows a strict diet to control his blood sugar level. The patient takes no medications. Blood pressure is 139/88 mm Hg and pulse is 70/min. Physical examination shows decreased lower-extremity sensation with a 10-g monofilament. His most recent hemoglobin A1c is 7.4% (normal, <5.6%). Serum creatinine is 1.0 mg/dL and serum potassium is 3.8 mEq/L. Further laboratory evaluation reveals increased urinary albumin excretion, but a conventional urinalysis is within normal limits. In addition to starting antihyperglycemic treatment, which of the following is the best pharmacotherapy for this patient?

A. Amlodipine
B. Carvedilol
C. Eplerenone
D. Hydrochlorothiazide
E. Isosorbide dinitrate
F. Lisinopril
G. Terazosin

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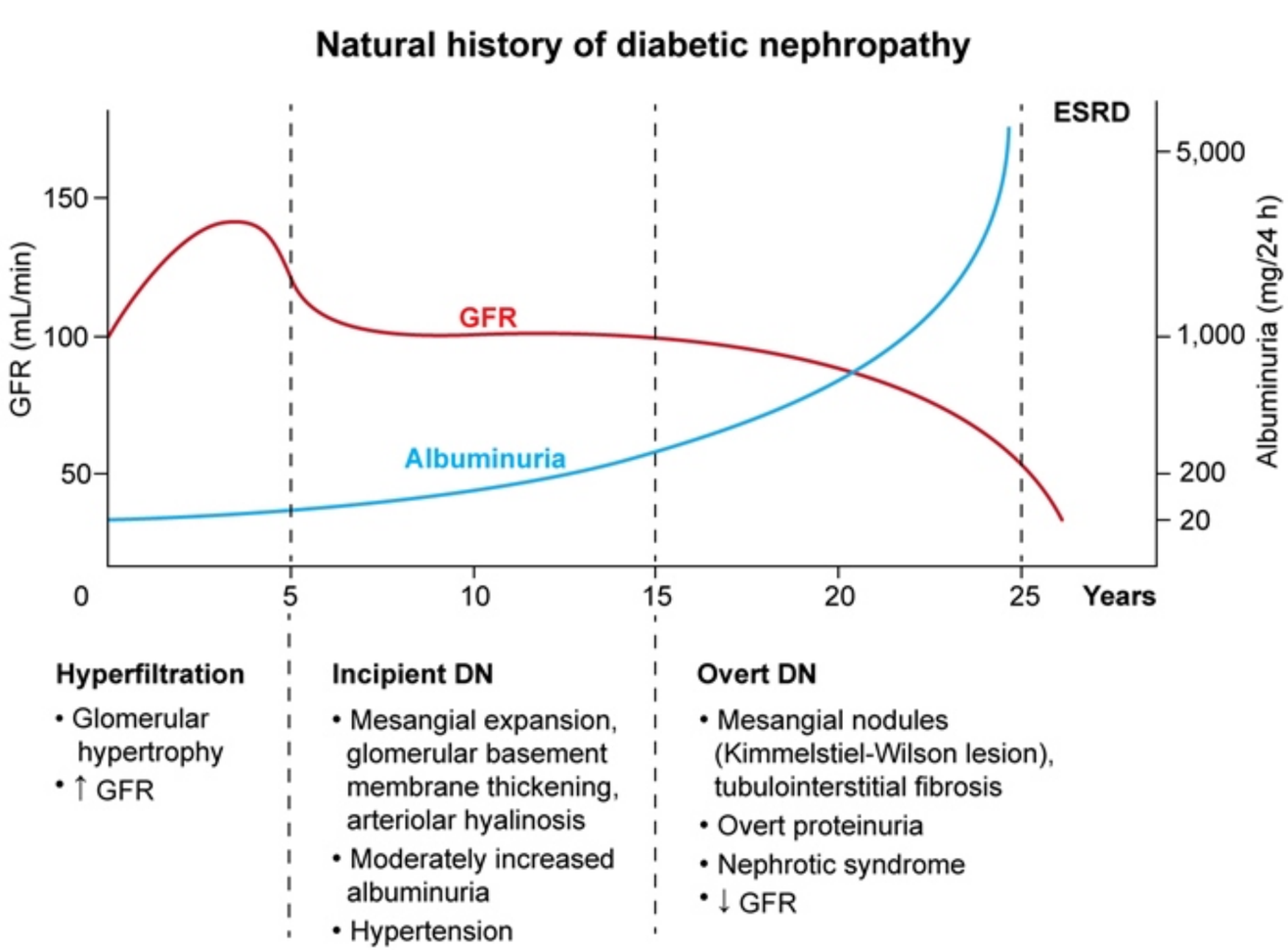

DN = diabetic nephropathy; **ESRD** = end-stage renal disease; **GFR** = glomerular filtration rate.
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This patient has diabetes mellitus complicated by neuropathy (decreased lower-extremity sensation) and nephropathy (increased urinary albumin excretion). **Moderately increased albuminuria** (also called microalbuminuria) is defined as urine albumin loss of 30-300 mg/day and is an early indication of **diabetic nephropathy** (DN). Microalbuminuria cannot be detected by standard dipstick urinalysis; only albumin excretion >300

This patient has diabetes mellitus complicated by neuropathy (decreased lower-extremity sensation) and nephropathy (increased urinary albumin excretion). **Moderately increased albuminuria** (also called microalbuminuria) is defined as urine albumin loss of 30-300 mg/day and is an early indication of **diabetic nephropathy** (DN). Microalbuminuria cannot be detected by standard dipstick urinalysis; only albumin excretion >300 mg/day (severely increased albuminuria) can be detected by conventional urinalysis. If left untreated, albuminuria is followed by progressive worsening of renal function leading to end-stage renal disease.

The progression of DN can be reduced by **glycemic and blood pressure control**. In addition, progression can be slowed by use of **ACE inhibitors** (eg, lisinopril) or angiotensin II receptor blockers. Early DN is characterized by elevated glomerular filtration pressure; angiotensin II further increases glomerular pressure by selective vasoconstriction of the efferent arteriole. Blockade of this angiotensin effect **lowers glomerular pressure**. Although ACE inhibitors decrease glomerular filtration in the short term, chronic use decreases albumin excretion and slows progression to overt renal failure. This benefit is independent of effects on systemic blood pressure and can also be seen in nonhypertensive patients.

(Choice A) Nondihydropyridine calcium channel blockers (eg, diltiazem, verapamil) decrease proteinuria, but this effect is not seen with dihydropyridine agents (eg, amlodipine, nifedipine). Although blood pressure control is important in patients with diabetes, lisinopril is more beneficial for preventing progression of nephropathy.

(Choices B and C) Carvedilol is a nonselective beta- and alpha-adrenergic blocker used in hypertension and congestive heart failure. Eplerenone is a mineralocorticoid (aldosterone) antagonist that is also used in congestive heart failure. These agents have no specific role in the management of DN.

(Choice D) Hydrochlorothiazide is an effective antihypertensive agent. However, it also causes hyperglycemia and may be associated with worsened glucose control in diabetic patients. ACE inhibitors are preferred over thiazides for first-line treatment.

(Choice E) Isosorbide dinitrate is an intermediate-acting nitrate used in the treatment of stable angina pectoris. It has no role in the management of DN.

(Choice G) Alpha-1 blockers (eg, doxazosin, prazosin, terazosin) are useful for treatment of hypertension and benign prostatic hyperplasia but are not recommended as monotherapy for hypertension due to an increased risk of cardiovascular events.

Educational objective:

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Educational objective:
The risk of progression of diabetic nephropathy in patients with proteinuria can be reduced by appropriate glycemic and blood pressure control. ACE inhibitors and angiotensin II receptor blockers are the preferred antihypertensive agents due to their antiproteinuric effects, which are independent from their effects on systemic blood pressure.

References

- Urinary biomarkers for early diabetic nephropathy in type 2 diabetic patients.
- Optimal strategies for identifying kidney disease in diabetes: properties of screening tests, progression of renal dysfunction and impact of treatment—systematic review and modeling of progression and cost-effectiveness.
- Prevalence of micro and macrovascular complications and their risk factors in type-2 diabetes mellitus.

Pharmacology	Renal, Urinary Systems & Electrolytes	Diabetic nephropathy
Subject	System	Topic

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A 68-year-old woman is brought to the emergency department due to worsening lethargy. Her family states that the patient has had headache and nausea for the past several days, and today she was confused and lethargic. Medical history is significant for a previous ischemic stroke with no residual neurologic deficit, seizure disorder, hypertension, type 2 diabetes mellitus, and bipolar disorder. Vital signs are within normal limits. On physical examination, the patient is somnolent and responds to painful stimuli only. Mucous membranes are moist and jugular venous pressure is normal. The lungs are clear to auscultation and heart sounds are normal. There is no extremity edema. Laboratory evaluation reveals serum sodium of 118 mEq/L; blood urea nitrogen and serum creatinine are within normal limits. Serum osmolality is low and urine osmolality is high. Which of the following medications is the most likely cause of this patient's condition?

A. Canagliflozin
B. Carbamazepine
C. Furosemide
D. Lithium
E. Spironolactone

Submit

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- A. Canagliflozin (7%)
- ✓ B. Carbamazepine (40%)
- C. Furosemide (11%)
- D. Lithium (32%)
- E. Spironolactone (7%)

Omitted
Correct answer
B

40%
Answered correctly

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02/24/2020
Last Updated

Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Low serum osmolality • High urine osmolality • High urine sodium

ADH = antidiuretic hormone; **JVD** = jugular venous distension; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **SSRIs** = selective serotonin reuptake inhibitors.

This patient has symptomatic hyponatremia (eg, somnolence, lethargy), and her laboratory studies (eg, low serum osmolality, high urine osmolality) are consistent with the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH). Antidiuretic hormone (ADH) secretion by the hypothalamus and posterior pituitary stimulates the renal collecting ducts to reabsorb water into the systemic circulation. This action lowers serum osmolality and sodium and increases extracellular volume. Patients with excessive ADH activity (ie, SIADH) typically have the following manifestations:

- Serum sodium and osmolality decrease, leading to **hypotonic hyponatremia**.
- Urinary water excretion decreases, increasing urine osmolality and creating a **concentrated urine**.

This patient has symptomatic hyponatremia (eg, somnolence, lethargy), and her laboratory studies (eg, low serum osmolality, high urine osmolality) are consistent with the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH). Antidiuretic hormone (ADH) secretion by the hypothalamus and posterior pituitary stimulates the renal collecting ducts to reabsorb water into the systemic circulation. This action lowers serum osmolality and sodium and increases extracellular volume. Patients with excessive ADH activity (ie, SIADH) typically have the following manifestations:

- Serum sodium and osmolality decrease, leading to **hypotonic hyponatremia**.
- Urinary water excretion decreases, increasing urine osmolality and creating a **concentrated urine**.
- **Clinical euvolemia**, which is reflected by an absence of edema, lung crackles, and jugular venous distention (signs of hypervolemia) along with absence of dry mucous membranes and elevated blood urea nitrogen (BUN) and creatinine (signs of hypovolemia).

In this case, the patient's SIADH is likely due to **carbamazepine**, an antiepileptic drug that induces ADH production and increases renal sensitivity to ADH. Other medications associated with SIADH include antidepressants (eg, selective serotonin reuptake inhibitors and tricyclic antidepressants), anticancer drugs (eg, cyclophosphamide), certain antidiabetic drugs (eg, chlorpropamide), and drugs of abuse (eg, MDMA [ie, ecstasy]).

(Choice A) Canagliflozin is a diabetic medication that inhibits sodium-glucose cotransporter 2 in the renal proximal tubule, increasing urinary glucose excretion. Canagliflozin is linked to urinary tract infections and hypotension, but not SIADH.

(Choices C and E) Furosemide and spironolactone are often used in combination to treat severe heart failure. Furosemide reduces sodium reabsorption in the loop of Henle, increasing sodium and water excretion. Spironolactone blocks the mineralocorticoid receptor, which increases sodium excretion and potassium reabsorption. Both diuretics can induce hyponatremia; however, patients are typically also hypovolemic (eg, with dry mucous membranes and elevated BUN and creatinine). This patient's euvolemia and normal BUN and creatinine are more consistent with SIADH.

(Choice D) Lithium can cause ADH resistance in the renal collecting ducts, resulting in nephrogenic diabetes insipidus. In this condition, water cannot be reabsorbed; urine osmolality is low (dilute urine) and serum sodium and osmolality increase. This patient has an opposite picture (high urine osmolality, low serum sodium and osmolality), indicating SIADH.

Educational objective:

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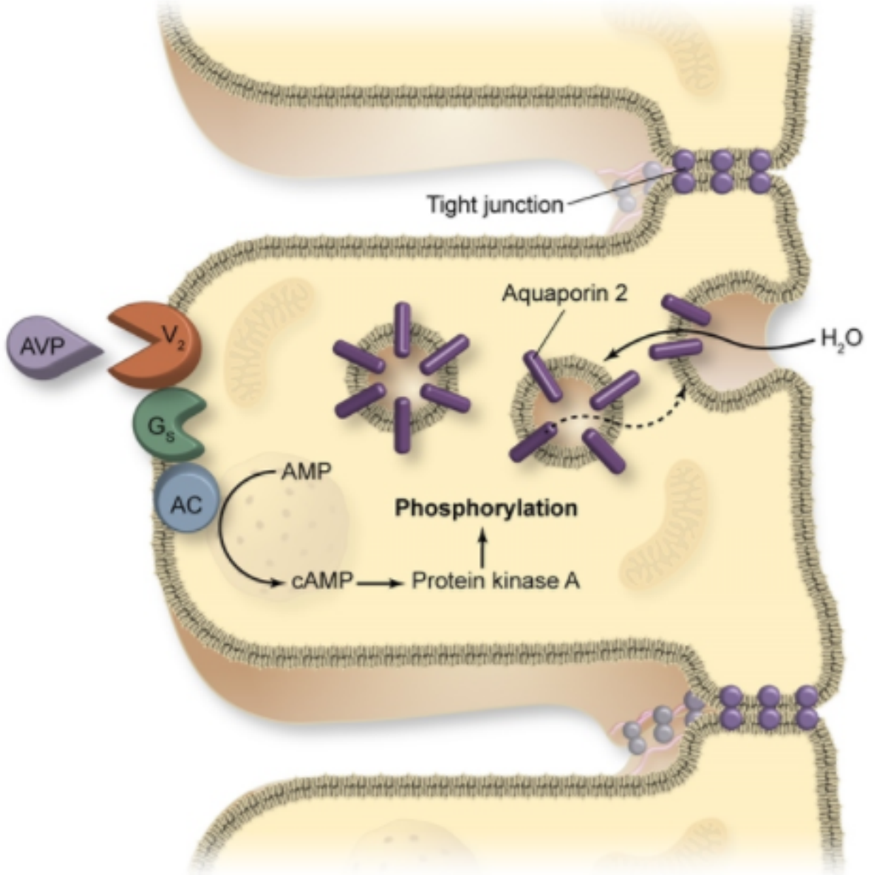
Exhibit Display

ADH action on collecting duct



AC = adenylyl cyclase; ADH = antidiuretic hormone; AVP = arginine vasopressin; cAMP = cyclic AMP.
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Educational objective:

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Educational objective:
The syndrome of inappropriate antidiuretic hormone (SIADH) presents with hypotonic hyponatremia (ie, low serum osmolality and serum sodium), concentrated urine (ie, high urine osmolality), and euvolemia. Carbamazepine can cause SIADH by increasing antidiuretic hormone (ADH) secretion and renal sensitivity to ADH.

References

- Hyponatremia associated with carbamazepine and oxcarbazepine therapy: a review.

Pharmacology	Renal, Urinary Systems & Electrolytes	SIADH
Subject	System	Topic

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A 27-year-old nursing assistant with a history of major depression and bulimia is brought to the emergency department after a suicide attempt. She claims to have ingested several diuretic pills 18 hours ago. The patient complains of frequent, large-volume urinations that started shortly after she ingested the pills. She has also been very thirsty but she denies nausea, vomiting, or diarrhea. Her temperature is 36.7 C (98 F), blood pressure is 96/60 mm Hg, pulse is 110/min, and respirations are 14/min. Physical examination shows dry oral mucosa and reduced skin turgor. Laboratory results are as follows:

Serum chemistry

Sodium	122 mEq/L
Potassium	2.8 mEq/L
Chloride	84 mEq/L
Bicarbonate	28 mEq/L
Blood urea nitrogen	22 mg/dL
Creatinine	1.4 mg/dL
Calcium	11.4 mg/dL
Albumin	3.9 g/dL

Which of the following medications did this patient most likely ingest?

A. Acetazolamide
B. Amiloride
C. Hydrochlorothiazide
D. Spironolactone

Laboratory results are as follows:

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C. Hydrochlorothiazide
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E. Torsemide

Submit

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Albumin	3.9 g/dL

Which of the following medications did this patient most likely ingest?

A. Acetazolamide (3%)
B. Amiloride (1%)
✓ C. Hydrochlorothiazide (78%)
D. Spironolactone (2%)
E. Torsemide (13%)

Omitted
Correct answer

78%
Answered correctly

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Time Spent

04/08/2020
Last Updated

Drug	Mechanism of action	Electrolyte abnormalities	Clinical indications
Loop diuretics • Furosemide • Torsemide • Bumetanide • Ethacrynic acid	Inhibits the Na-K-2Cl cotransporter in the thick ascending limb of loop of Henle	• Hypokalemia • Metabolic alkalosis • Hypocalcemia	Volume-overloaded states (eg, congestive heart failure)
Thiazide diuretics • Hydrochlorothiazide • Chlorthalidone • Indapamide • Metolazone	Inhibits the Na-Cl cotransporter in the early distal convoluted tubule	• **Hyponatremia** • Hypokalemia • Metabolic alkalosis • **Hypercalcemia**	• Hypertension • Calcium nephrolithiasis prophylaxis
Carbonic anhydrase inhibitors • Acetazolamide	Inhibits carbonic anhydrase enzyme in the proximal tubule	• Hypokalemia • **Metabolic acidosis**	• Refractory metabolic alkalosis • Intracranial hypertension
Sodium channel blockers • Amiloride • Triamterene	Inhibits the apical ENaC channel in the cortical collecting duct	• **Hyperkalemia** • Metabolic acidosis	Often used in synergy with loop & thiazide diuretics to limit potassium loss
Mineralocorticoid receptor antagonists	Inhibits the apical ENaC channel & basolateral Na-K-		

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Sodium channel blockers • Amiloride • Triamterene	Inhibits the apical ENaC channel in the cortical collecting duct	• **Hyperkalemia** • Metabolic acidosis	Often used in synergy with loop & thiazide diuretics to limit potassium loss
Mineralocorticoid receptor antagonists • Spironolactone • Eplerenone	Inhibits the apical ENaC channel & basolateral Na-K-ATPase pump in the cortical collecting tubules		

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Loop diuretics are the most potent type of diuretic, followed by thiazide diuretics. Administration of either agent initially results in natriuresis. However, continued use leads to significant volume depletion that counteracts the diuretic effect by decreasing glomerular filtration pressure. Reduced pressure natriuresis also decreases distal tubule Na^+ delivery, which is sensed by the macula densa and causes activation of the renin-angiotensin-aldosterone system. Aldosterone then acts on the collecting tubule to enhance Na^+ reabsorption and promote K^+ and H^+ loss. Therefore, **loop and thiazide diuretics** cause **hypokalemia** and **metabolic alkalosis** secondary to volume contraction.

Loop diuretics function by inhibiting the absorption of solutes within the thick ascending limb of Henle's loop, a process that is critical for maintenance of the corticomedullary concentration gradient. As a result, patients on loop diuretics are unable to maximally concentrate their urine and thus lose substantial amounts of both salt and water in the urine. In contrast, patients taking thiazides have a normal corticomedullary concentration gradient and are better able to retain free water in response to increased vasopressin levels. Thus, patients taking **thiazide**

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Thiazide diuretics can also lead to **hypercalcemia** secondary to increased proximal and distal tubule Ca^{2+} reabsorption. In contrast, loop diuretics decrease Ca^{2+} reabsorption in the thick ascending limb and can cause hypocalcemia **(Choice E)**.

(Choice A) Acetazolamide induces a mild degree of natriuresis by inhibiting bicarbonate reabsorption in the proximal tubule. The loss of bicarbonate in the urine also causes metabolic acidosis in addition to inducing natriuresis.

(Choices B and D) Amiloride and spironolactone are potassium-sparing diuretics that induce a mild degree of natriuresis. By decreasing Na^+ reabsorption in the cortical collecting tubule, they reduce the luminal electronegative gradient, a major driving force for K^+ and H^+ secretion by principal and intercalated cells, respectively. As a result, potassium-sparing diuretics can cause hyperkalemia and metabolic acidosis.

Educational objective:
Thiazide and loop diuretics cause significant volume depletion, activating the renin-angiotensin-aldosterone system, which can lead to hypokalemia and metabolic alkalosis. Thiazide diuretics are more likely to cause hyponatremia and hypercalcemia; loop diuretics cause hypocalcemia.

References

- Diuretic therapy.

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A 64-year-old man comes to the office after learning at the dentist's office that he has elevated blood pressure. The patient is a combat veteran and has always been "fit as a bull." He has undergone various minor surgical procedures for wartime injuries. He reports many years of tobacco and alcohol use but currently uses neither. On careful questioning, he describes chest pain on exertion. Blood pressure is 155/90 mm Hg and pulse is 76/min. Physical examination is significant for decreased pulse amplitude over the right femoral artery and a systolic bruit over the left carotid artery. Resting ECG is unremarkable, and serum creatinine is 1.1 mg/dL. Urinalysis is negative for protein. Treatment for hypertension is initiated with ramipril. On a follow-up visit 3 weeks later, blood pressure is 142/85 mm Hg but serum creatinine has increased to 2 mg/dL. This laboratory finding is best explained by an effect of the drug on which of the following structures (as indicated in the image)?

A. A
B. B
C. C
D. D
E. E

Submit

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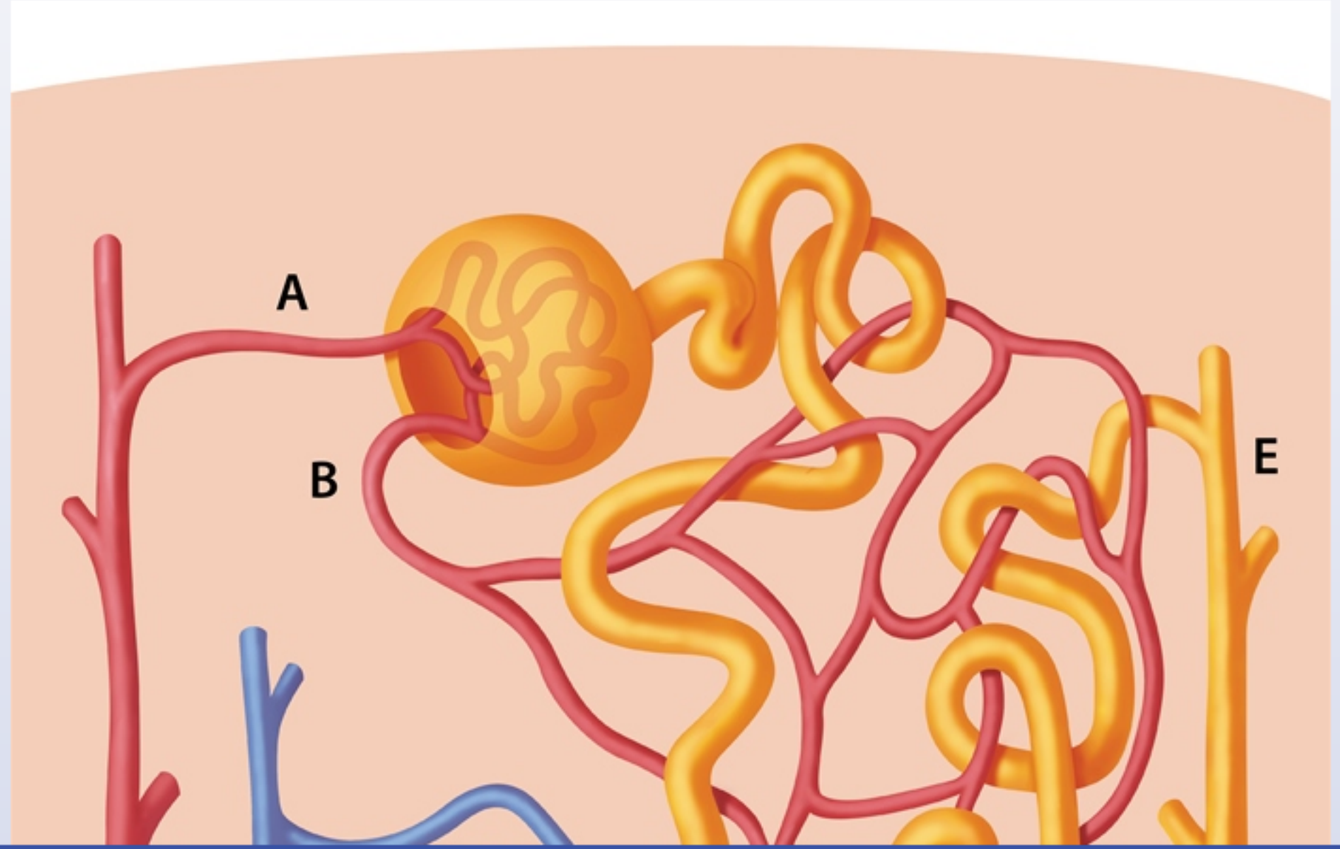

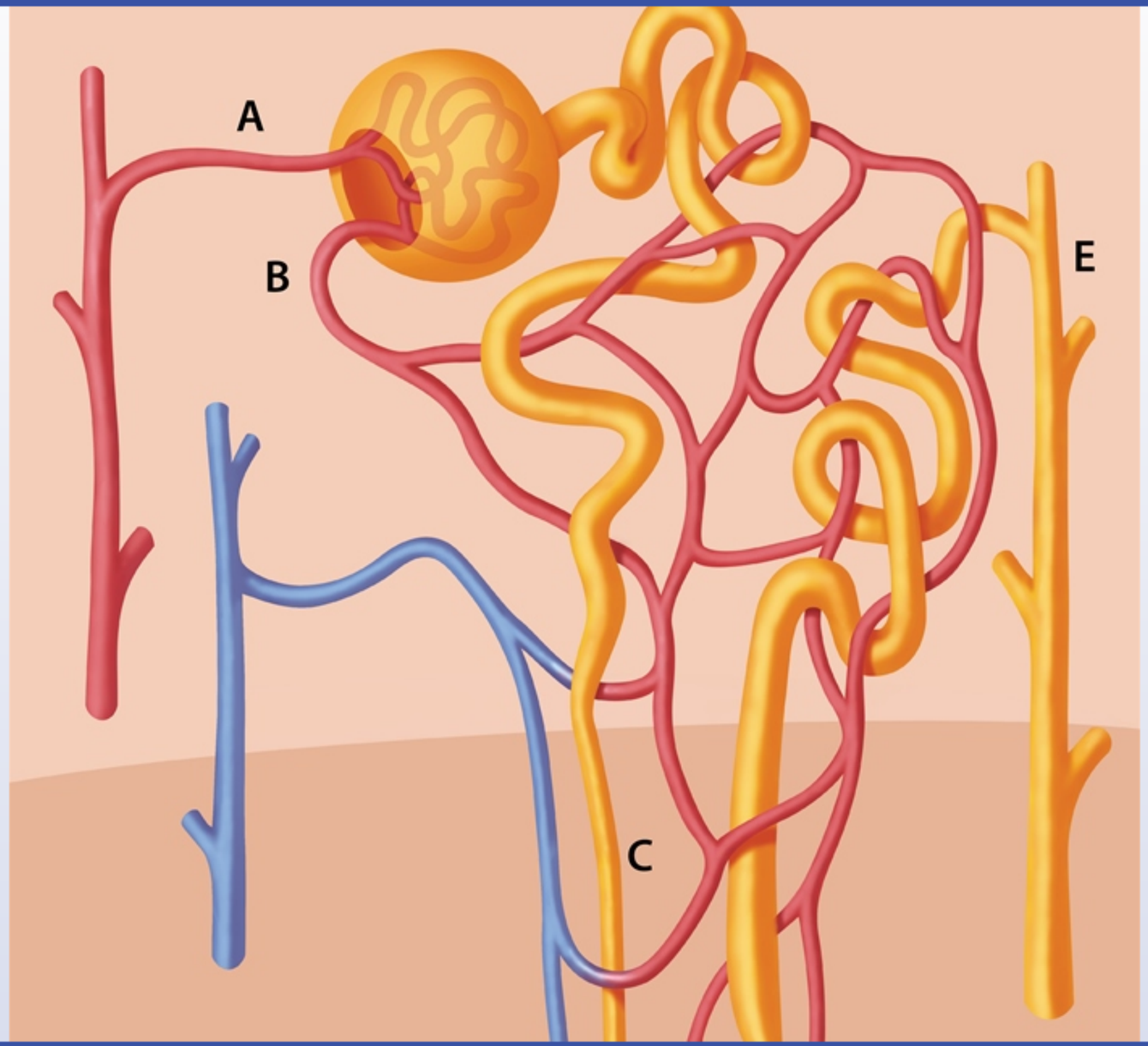
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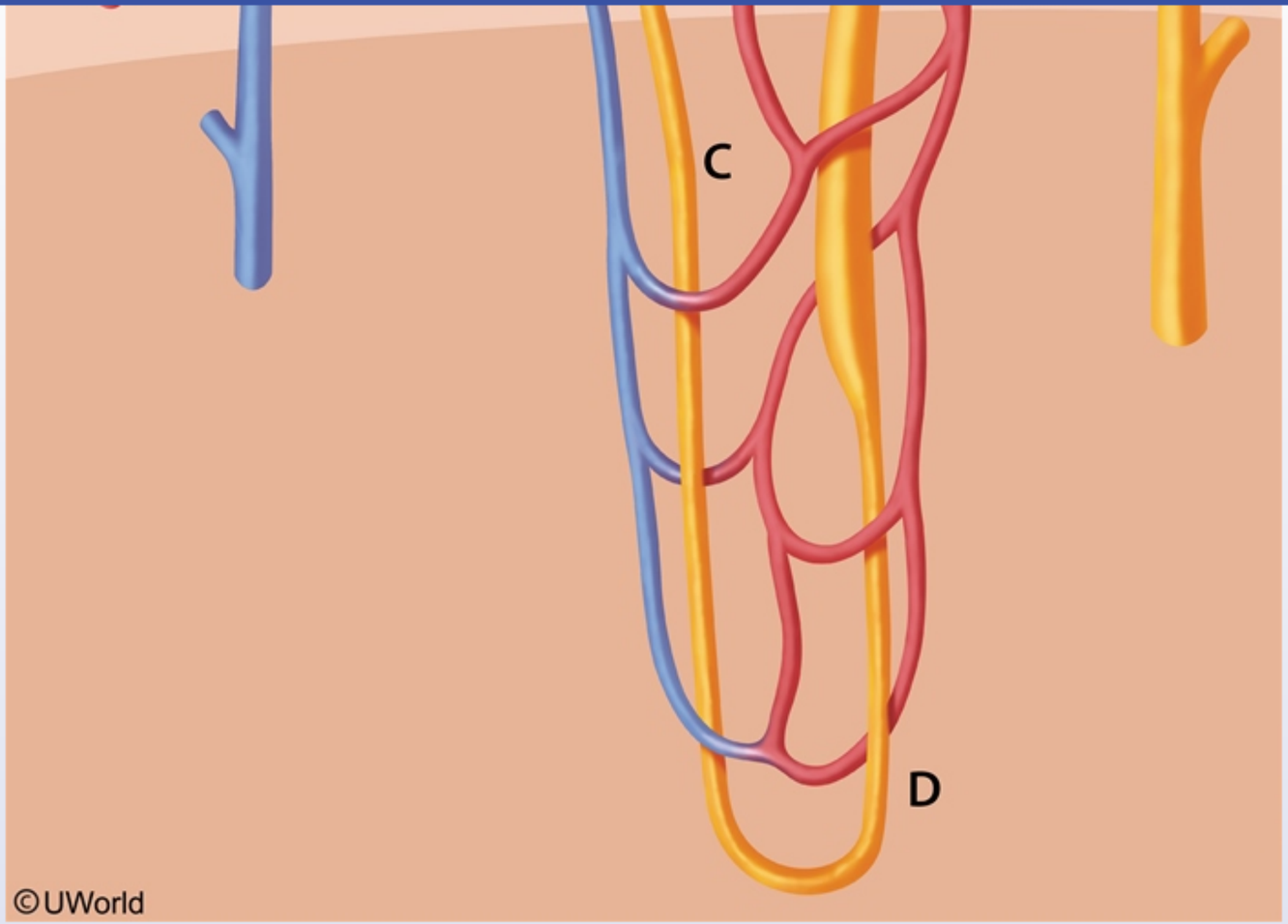

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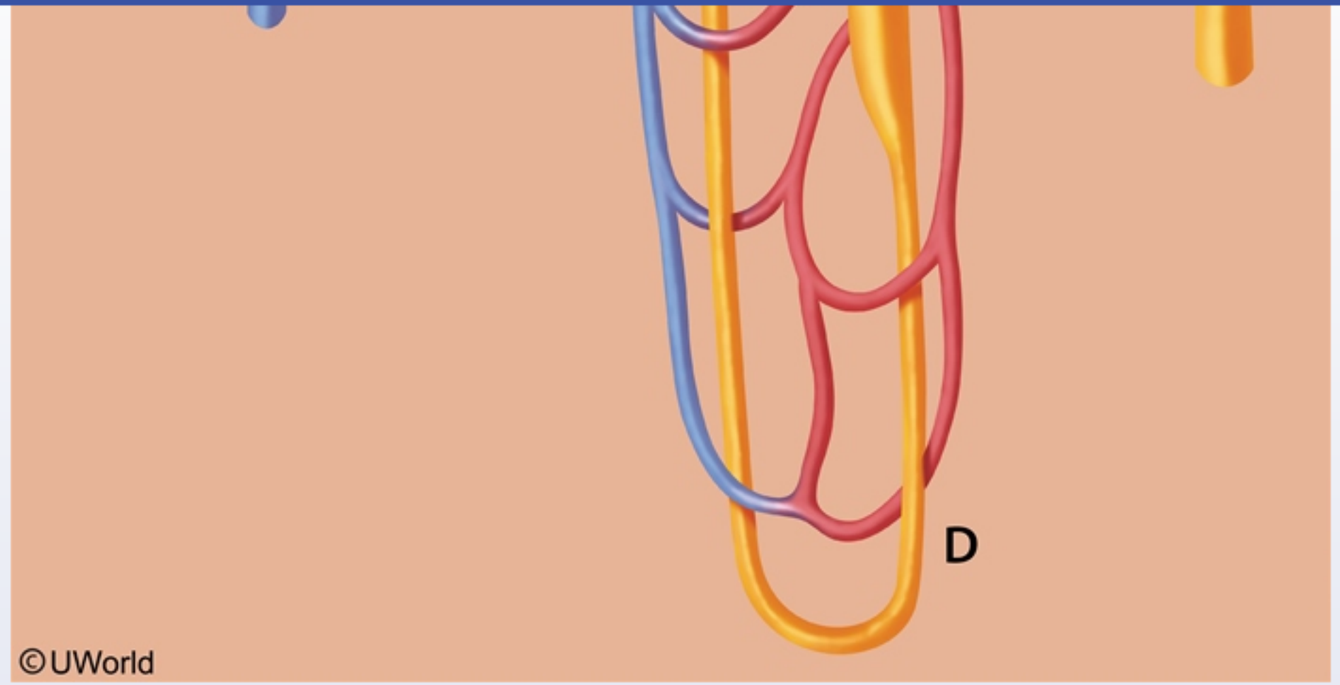

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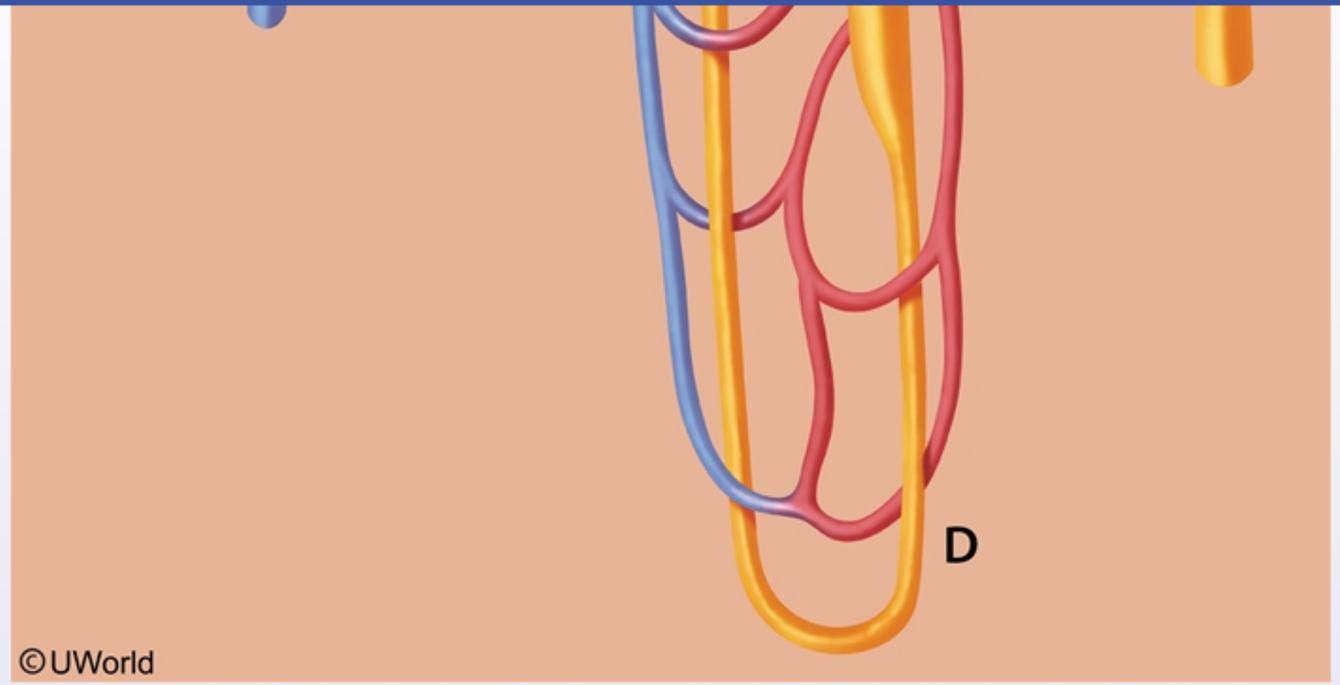

A. A (14%)
B. B (77%)
C. C (1%)
D. D (1%)
E. E (5%)

Omitted
Correct answer

77%
Answered correctly

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01/24/2020
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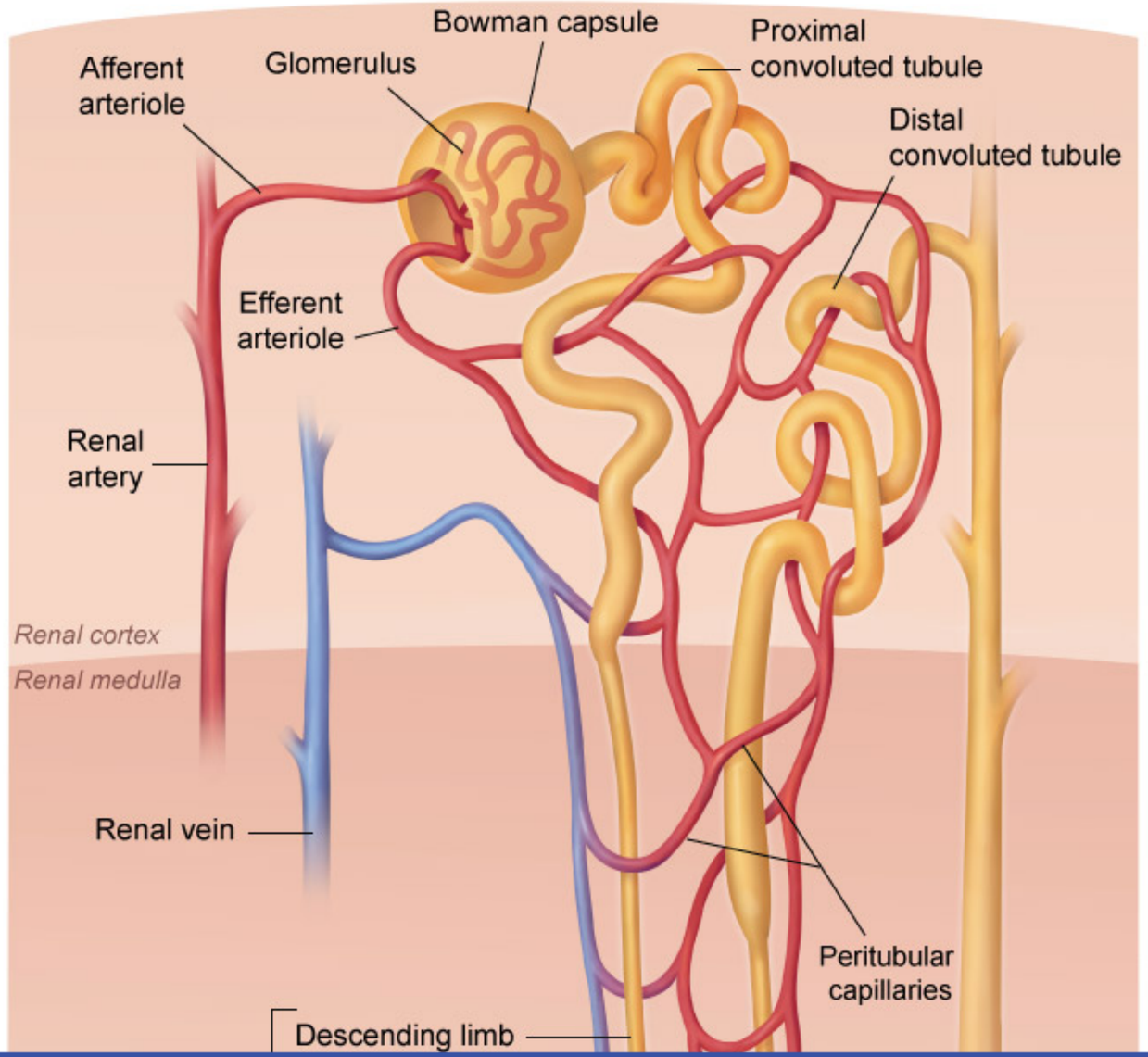
Nephron



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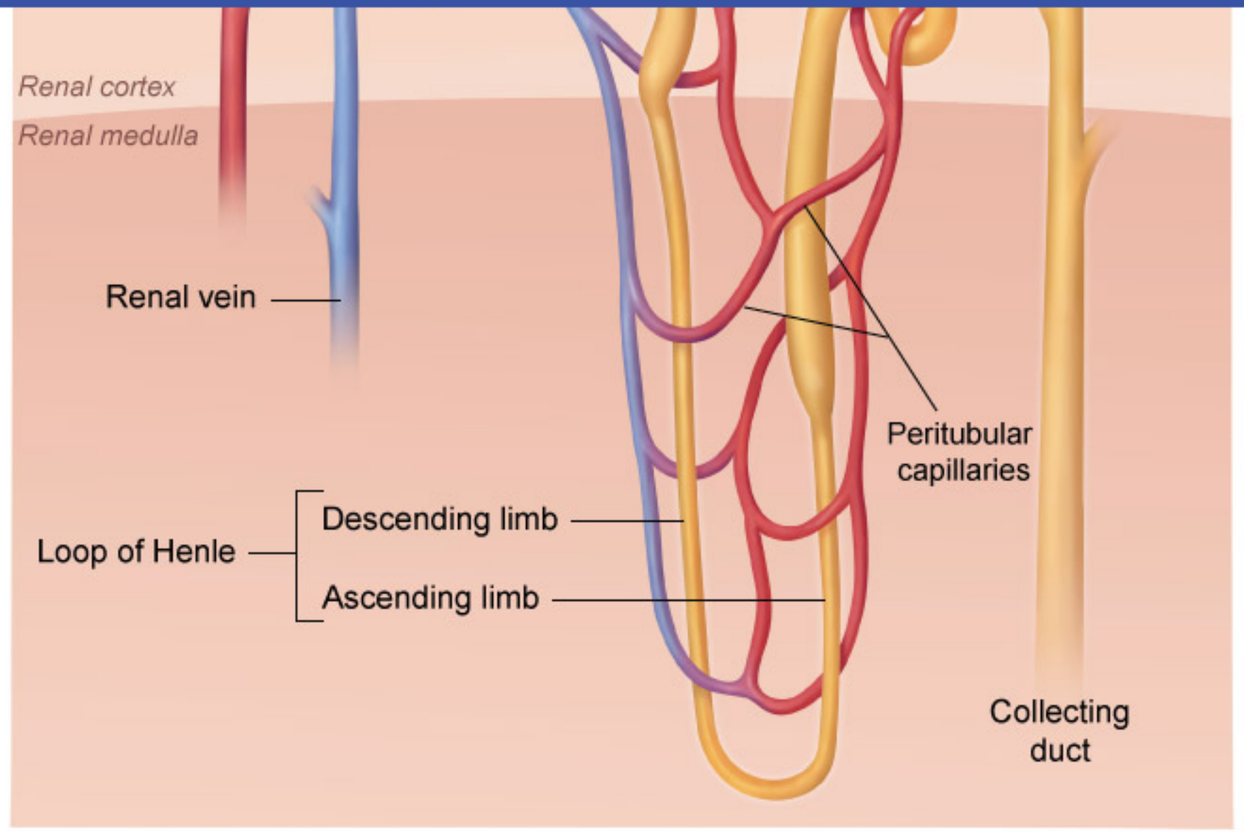

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This patient with angina, reduced femoral pulsation, and a carotid bruit has diffuse atherosclerosis. Patients with severe atherosclerosis or atherosclerotic risk factors (eg, hypertension, hyperlipidemia, smoking) are more likely to develop atherosclerotic **renal artery stenosis** (RAS). Conditions that reduce renal perfusion (eg, hypovolemia, congestive heart failure, RAS [as in this patient]) lower glomerular filtration pressure and the glomerular filtration rate (GFR), stimulating the renin-angiotensin-aldosterone system. This results in increased levels of **angiotensin II**, a potent vasoconstrictor that causes systemic hypertension and preferentially **constricts the efferent arteriole** to restore GFR.

ACE inhibitors lower angiotensin II levels, causing systemic vasodilation and reduced blood pressure. However, they also cause **efferent arteriolar dilation** and lower intraglomerular pressure, preventing the kidney from maintaining GFR in the setting of reduced renal perfusion.

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ACE inhibitors lower angiotensin II levels, causing systemic vasodilation and reduced blood pressure. However, they also cause **efferent arteriolar dilation** and lower intraglomerular pressure, preventing the kidney from maintaining GFR in the setting of reduced renal perfusion. Many patients experience up to a 30% increase in serum creatinine within 2-5 days of starting ACE inhibitors. Patients with bilateral RAS (who are heavily dependent on angiotensin II to maintain GFR) can experience a precipitous fall in GFR and develop **acute renal failure**.

(Choice A) Locally produced vasodilators (prostaglandins and nitric oxide) in the afferent arteriole counteract the vasoconstrictive effects of angiotensin II; as a result ACE inhibitors do not significantly affect the afferent arterioles. However, nonsteroidal anti-inflammatory drugs (eg, ibuprofen) and calcineurin inhibitors (eg, cyclosporine) inhibit prostaglandin formation, resulting in constriction of the afferent arterioles and a reduction in intraglomerular pressure.

(Choices C and D) Aminoglycosides, vancomycin, certain antiretrovirals (eg, cidofovir), and foscarnet can damage the renal tubular cells, resulting in acute tubular necrosis. However, ACE inhibitors are not directly toxic to the renal tubules and have no effect on the descending or ascending loop of Henle.

(Choice E) ACE inhibitors block the release of aldosterone, resulting in decreased Na^+ reabsorption and K^+ secretion in the distal and collecting tubules. Although this effect is responsible for the hyperkalemia often seen with ACE inhibitor therapy, it would not cause the rise in creatinine.

Educational objective:
ACE inhibitors reduce angiotensin II levels and cause efferent arteriole dilation, thereby decreasing the glomerular filtration pressure and filtration rate. This can precipitate acute renal failure in patients with reduced intrarenal perfusion pressure at baseline (eg, renal artery stenosis, congestive heart failure, hypovolemia).

Pharmacology	Renal, Urinary Systems & Electrolytes	ACE inhibitors

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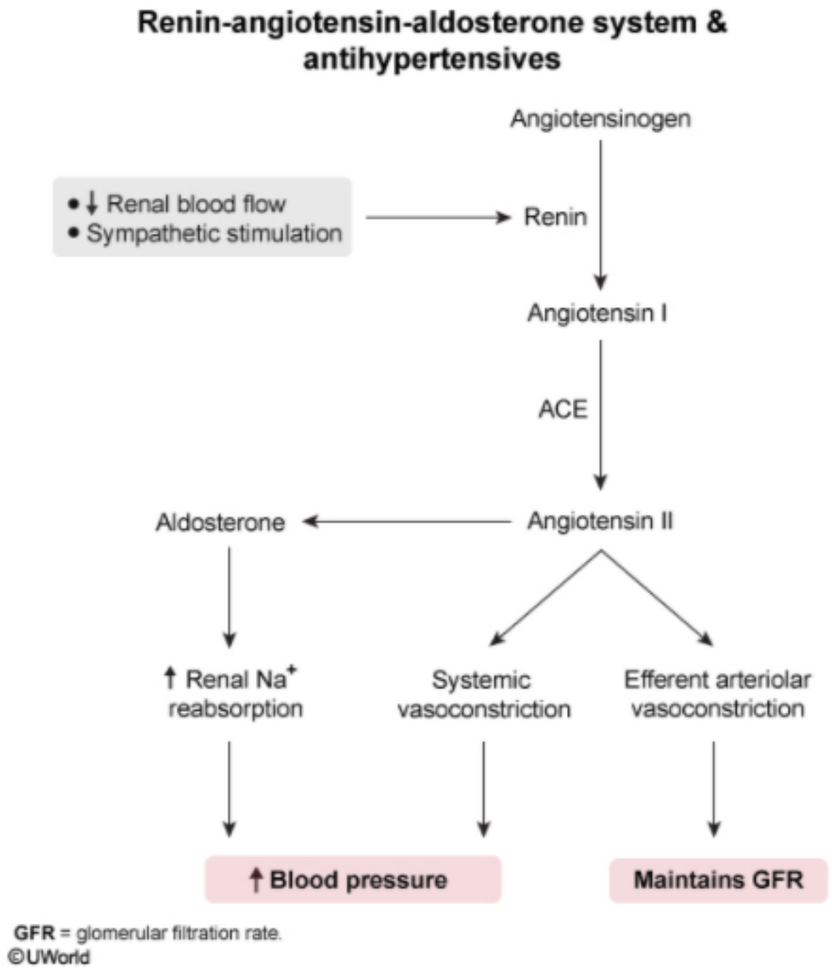
Exhibit Display



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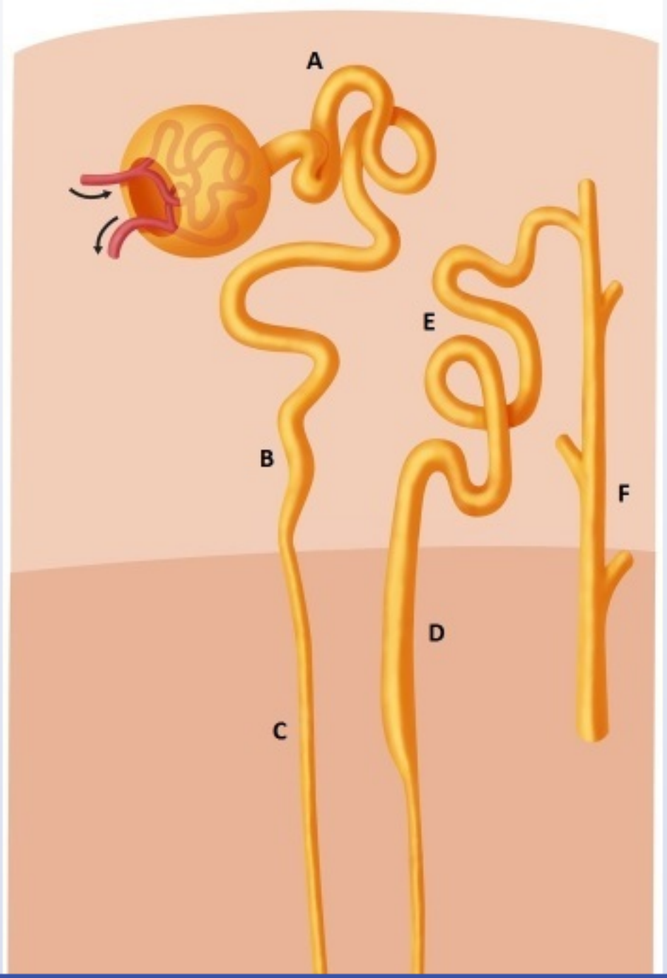
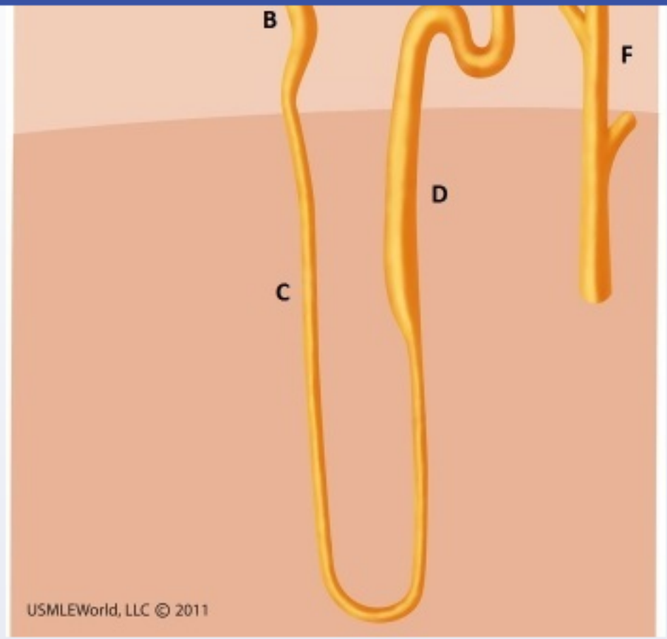
A 62-year-old man comes to the physician for a follow-up appointment. He experienced acute myocardial infarction 2 years ago and has a long history of hypertension. After physical examination and laboratory testing, the physician decides to increase the dose of his diuretic. Repeat laboratory studies indicate that his serum calcium level increases after this adjustment. The diuretic used in this patient acts predominantly on which of the following nephron segments?





A. A
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D. D
E. E
F. F

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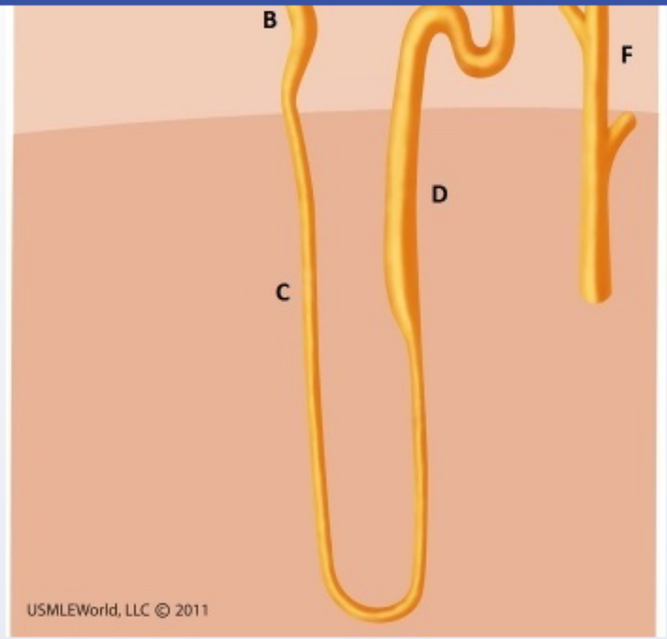

A. A (3%)
B. B (1%)
C. C (1%)
D. D (8%)
✓ E. E (83%)
F. F (1%)

Omitted
Correct answer

83%
Answered correctly

05 secs
Time Spent

05/13/2020
Last Updated

Major side effects of commonly used diuretics	
Loop diuretics *furosemide, bumetanide, torsemide*	Hypokalemia, hypomagnesemia, hypocalcemia, and ototoxicity
Thiazide diuretics *chlorthalidone, hydrochlorothiazide*	Hypokalemia, hyponatremia, **hyperuricemia**, and **hypercalcemia**
Potassium sparing diuretics *triamterene, spironolactone*	*All:* hyperkalemia *Spironolactone:* gynecomastia, antiandrogen effects
Carbonic anhydrase inhibitors *acetazolamide*	Metabolic acidosis
Osmotic diuretics *mannitol*	Hypernatremia, pulmonary edema

Thiazide diuretics work in the distal convoluted tubule, causing enhanced Na^+, Cl^-, and water excretion. The apical membrane of early distal tubule cells contains the Na^+/Cl^- symporter while the basolateral side has Na^+/K^+ ATPases and Cl^- channels that maintain a NaCl gradient across the apical cell membrane. Thiazides inhibit the apical Na^+/Cl^- symporter, decreasing luminal NaCl absorption into the distal tubular cell. This can cause hypercalcemia by reducing intracellular Na^+ concentrations, which in turn increases the activity of the basolateral Na^+-Ca^{2+} exchanger. The resulting reduction in intracellular Ca^{2+} levels acts to increase luminal Ca^{2+} absorption in the distal tubule. Increased Ca^{2+} absorption in the proximal tubule secondary to volume depletion can also contribute to hypercalcemia in thiazide-treated patients.

There are a number of thiazide and thiazide-like diuretics available. Examples include hydrochlorothiazide, chlorothiazide, indapamide, and metolazone. They differ in potency, bioavailability, and half-life. Thiazides are not as efficacious as loop diuretics as only a small amount of filtered Na reaches the distal tubules. They are used to treat edema secondary to heart failure, renal disease, and liver disease. Thiazides are also commonly used to treat hypertension. More common side effects include hypokalemia, hyponatremia, and hypomagnesemia. Less common

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(Choices A and B) Carbonic anhydrase inhibitors block the reabsorption of $NaHCO_3$ and work in the convoluted and straight portions of the proximal tubule.

(Choice C) Osmotic diuretics such as mannitol function mainly in the proximal tubule and the descending limb of the loop of Henle to reduce Na and water reabsorption.

(Choice D) Loop diuretics work in the thick ascending limb and are the most potent diuretics.

(Choice F) The collecting duct system includes the connecting tubules and ducts. Here, aldosterone and ADH make final adjustments to electrolytes and water content. Potassium- sparing diuretics and aldosterone antagonists work in the collecting duct.

Educational objective:
Thiazide diuretics work by blocking Na^+-Cl^- symporters in the distal convoluted tubules, causing enhanced Na, Cl, and water excretion. Since only a small amount of filtered Na^+ reaches the distal tubules, thiazides are not as efficacious as loop diuretics. Unlike loop diuretics, thiazides can cause hypercalcemia.

References

- Thiazide-induced hypocalciuria is accompanied by a decreased expression of Ca2+ transport proteins in kidney.

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Pharmacology	Renal, Urinary Systems & Electrolytes	Thiazides
Subject	System	Topic

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A 64-year-old man comes to the office for follow-up. He has a history of chronic kidney disease due to hypertensive and diabetic nephropathy. Six months ago, he developed significant fatigue and exercise intolerance. Evaluation at that time revealed normocytic anemia and normal serum iron studies so recombinant erythropoietin was initiated. Today, the patient states that his symptoms have significantly improved. Laboratory evaluation reveals a hemoglobin of 12 g/dL. If the erythropoietin treatment is continued, this patient is at greatest risk for which of the following complications?

- A. Autoimmune hemolysis
- B. Bone marrow fibrosis
- C. Gallstone formation
- D. Iron overload
- E. Venous thrombosis

Submit

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- A. Autoimmune hemolysis (1%)
- B. Bone marrow fibrosis (7%)
- C. Gallstone formation (4%)
- D. Iron overload (12%)
- ✓ E. Venous thrombosis (74%)

Omitted
Correct answer
E

74%
Answered correctly

02 secs
Time Spent

06/17/2020
Last Updated

Explanation

Erythropoietin (EPO) promotes the survival, differentiation, and proliferation of immature erythrocytes. It is produced by interstitial fibroblasts near the peritubular capillaries of the kidney in response to hypoxia; **deficiency** often occurs in the setting of chronic kidney disease due to inflammatory damage to the peritubular interstitial fibroblasts.

Patients with EPO deficiency generally present with **normocytic anemia**, low reticulocyte count, and iron studies similar to those seen in anemia of chronic disease (eg, low serum iron, low/normal total iron-binding capacity). Treatment with **recombinant EPO** restores the stimulus for

Explanation

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Patients with EPO deficiency generally present with **normocytic anemia**, low reticulocyte count, and iron studies similar to those seen in anemia of chronic disease (eg, low serum iron, low/normal total iron-binding capacity). Treatment with **recombinant EPO** restores the stimulus for erythropoiesis, **increases hemoglobin**, and improves tissue oxygen delivery. However, **prolonged use** of EPO can lead to serious morbidity, including the following:

- **Thromboembolism:** EPO increases blood viscosity and triggers the release of proinflammatory cytokines from the endothelium, which increases the risk for thromboembolism. It also promotes the release of procoagulant proteins such as von Willebrand factor and plasminogen activator inhibitor-1.
- **Hypertension:** EPO increases systemic vascular resistance, possibly due to activation of erythropoietin receptors on vascular endothelial and smooth muscle cells. This can result in hypertensive encephalopathy and increased risk of **cardiovascular events** (eg, stroke, myocardial infarction).

To avoid morbidity, most studies recommend **cessation** of recombinant EPO once hemoglobin improves to **12-13 g/dL**; attempting to increase hemoglobin >13 g/dL increases the risk of adverse effects and death.

(Choice A) Autoantibodies can form against recombinant EPO, which limits its efficacy. However, recombinant EPO does not typically trigger autoantibodies against erythrocytes; therefore, hemolytic anemia would be atypical.

(Choice B) Recombinant EPO may worsen malignancy due to the promotion of vascular growth. It does not typically cause myelofibrosis or myeloproliferative disorders. However, these conditions may be triggered by the use of granulocyte colony–stimulating hormone due to excessive stimulation of granulocyte stem cells.

(Choice C) The use of recombinant EPO does not usually increase bilirubin and does not typically cause gallstones. Increased risk of gallstones can be seen with some causes of anemia such as sickle cell disease and thalassemia.

(Choice D) Recombinant EPO stimulates erythrocytosis, which can rapidly consume iron stores (it does not cause iron overload). Therefore, iron

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(Choice D) Recombinant EPO stimulates erythrocytosis, which can rapidly consume iron stores (it does not cause iron overload). Therefore, iron levels should be monitored before and during treatment to ensure that iron deficiency does not occur.

Educational objective:
Patients with chronic kidney disease often develop normocytic anemia due to erythropoietin (EPO) deficiency. Treatment with recombinant EPO can dramatically improve tissue oxygen delivery and reduce mortality. However, prolonged or high-dose treatment can have serious side effects, most notably increased risk of hypertension and thromboembolism.

References

- Clinical use of erythropoietin in chronic kidney disease: outcomes and future prospects.

Pharmacology	Renal, Urinary Systems & Electrolytes	Erythropoietin
Subject	System	Topic

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